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RECYCLIZATION OF 2,2-DISUBSTITUTED 4(3H)-OXO- AND 4-CHLORO-1,2-DIHYDROPYRIMIDINES TO 4-AMINOPYRIDINE DERIVATIVES

A. V. Upadysheva, N. D. Grigor'eva, Yu. S. Ryabokobylko, and A. P. Znamenskaya

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The intramolecular cationotropic rearrangement of salts of two-ring 2,2-disubstituted 4-chloro-1,2-dihydropyrimidines to 4-aminopyridine derivatives was observed. Recyclization to 4-aminopyridines can take place in the reaction of two-ring 2,2-disubstituted 4(3H)-oxo-1,2-dihydropyrimidines with phosphorus oxychloride without isolation of the intermediate chloro derivatives. A probable mechanism that makes it possible to assert that the observed recyclization is a variant of the intramolecular cationotropic rearrangement that is characteristic for 2,2-dialkyl-substituted 1,2-dihydropyrimidines with functional substituents (for example, oxo or chloro) in the 4 position of the ring is discussed.

It is known that 2,2-disubstituted 4(3H)-oxo-1,2-dihydropyrimidines I under the influence of polyphosphoric acid (PPA) at 135°C undergo cationotropic rearrangement to give 2-pyridone derivatives in good yields and 4-oxo- and 4-aminopyridine derivatives in very small amounts [1].

We assumed that 2,2-disubstituted 4-chloro-1,2-dihydropyrimidines are also capable of undergoing similar transformations. In fact, instead of the usual chloro derivatives of 1,2-dihydropyrimidine, 4-aminopyridine derivatives II with known structures [2, 3] are formed in 38-85% yields in the reaction of I with an eightfold to tenfold excess of phosphorus oxychloride (by refluxing in toluene for 10-24 h).

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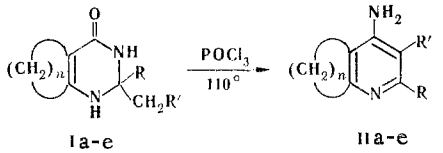


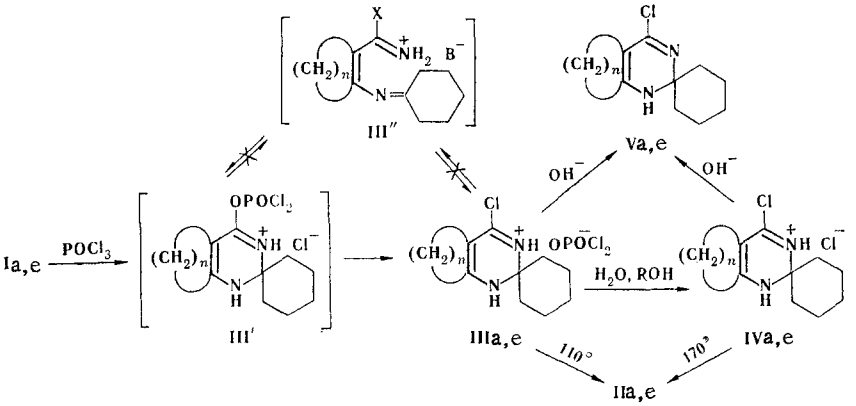
Ia-e IIa-e

I, II a-d $n=3$; a $R+R'=(CH_2)_4$; b $R+R'=(CH_2)_3$; c $R+R'=(CH_2)_5$; d $R=R'=CH_3$, e $n=4$; $R+R'=(CH_2)_4$

A study of the products of the reaction of 4-oxodihydropyrimidines Ia, e with the same excess amounts of $POCl_3$ but for shorter reaction times (2-8 h) showed that, in addition to 4-aminopyridine derivatives IIa, e, the expected primary reaction products, viz., 2,2-disubstituted 4-chloro-1,2-dihydropyrimidine salts IIIa, e, are also formed. The maximum yields of IIIa, e were obtained for a reaction time of 1 h; the yields of III decreased, while the yields of II increased, when the reaction time was increased. We investigated the structure of intermediate salts III and their ability to undergo conversion to 4-aminopyridine derivatives II.

Considering the peculiarities of the reaction of amides with phosphorus oxychloride [4] and the possibility of opening of the pyrimidine ring [1] of the initially formed III' cation, one might have proposed several alternative structures (III, III', and III") structures for the isolated salts.

Strong νP—C absorption bands at 530 cm^{-1} and νP=O absorption bands at 1295 cm^{-1} of the ionic $OPOCl_2^-$ group are observed in the IR spectra of salts IIIa, e, but a νP—O—C band at 1190-1240 cm^{-1} [5] is absent.



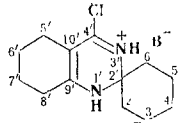
a $n=3$; e $n=4$; III" X=$OPOCl_2$, B=Cl; or X=Cl, B=$OPOCl_2$

A broad (with several maxima) absorption band due to νNH and $\nu\overset{+}{N}H-$ vibrations and their interaction with other vibrations is observed at 2500-3200 cm^{-1}. In the ^{13}C NMR spectrum of salt IIIe the signal of the C_2 atom is found at δ71.1 ppm (Table 1), which unambiguously indicates sp^3 hybridization of this atom, i.e., the cyclic structure of III. Signals of protons at 9.8 and 10.15 ppm, which were assigned to the protons attached to the N_1 and N_3 atoms, are observed in the PMR spectrum of IIIe (Table 1).

In water or in alcohol solutions dichlorophosphoryl salts III undergo gradual hydrolysis to hydrochloride salts IV. The IR, PMR, and ^{13}C NMR spectra of salt IVe are similar to the corresponding spectra of salt IIIe. The signals of the C_4' atom, which are found at 166.0 ppm in the spectrum of dichlorophosphoryl salt IIIe and at 165.6 ppm in the spectrum of hydrochloride IVe, confirm that identical functional substituents are present in the 4 position of the pyrimidine ring in these salts.

Salts III and IV are quite soluble in chloroform and acetone and almost insoluble in water. The high solubilities of salts III and IV in solvents with low polarities make it possible to assume that they are intimate ion pairs. The appreciable change in the chemical shift of the proton in the 5' position of the pyrimidine cation as a function of the anion confirms this assumption (Table 1).

Salts III and IV readily undergo recyclization to 4-aminopyridine derivatives II in

TABLE 1. Parameters of the PMR and ^{13}C NMR Spectra of 

Compound	PMR spectrum, δ, ppm						^{13}C NMR spectrum, δ, ppm								
	1′-H	3′-H	5′-H	8′-H	6′-H, 7′-H	C_6H_{10}	2′-C	4′-C	10′-C	9′-C	5′-C	6′-C	7′-C	8′-C	2-C, 3-C, 4-C, 6-C, and 5-C substituents
IIIe[a]	9,80 s (1H)	10,15 s (1H)	2,69 m (2H)	2,36m (2H)	2,02m (4H)	1,50—1,75m (10H)	71,1	166,0	100,3	153,3	22,8	20,5[b]	21,5	27,9	33,2 20,1 24,2
IVe	10,39s (1H)	10,53 s (1H)	2,85m (2H)	2,38 m (2H)	2,07m (4H)	1,45—1,80m (10H)	72,0	165,6	100,7	154,6	23,3	20,9[b]	22,1	28,5	33,4 20,9 24,9

[a]The ^{13}C NMR spectrum of IIe was recorded in d_6-DMSO, while the remaining spectra were recorded in $CDCl_3$; B = $OPOCL_2$ for IIIe, while B = Cl for IVe. [b]The assignment may be just the opposite.

TABLE 2. Characteristics of the Synthesized Compounds

Compound	mp, °C	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, ν, cm^{-1}	Found, %					Empirical formula	Calc., %					Yield, %
				C	H	Cl	N	P		C	H	Cl	N	P	
IIIa	134—136	365 (3,73)	530, 740, 1295, 1538, 1648, 2500—3040, 3090	40,1	5,0	29,3	7,8	8,8	$C_{12}H_{17}ClN_2 \cdot HPO_2Cl_2$	40,1	5,0	29,6	7,8	8,6	50
IIIe	142,5—144	365 (3,70)	537, 765, 1296, 1530, 1560, 2500—3200	41,7	5,2	28,7	7,5	8,5	$C_{13}H_{19}ClN_2 \cdot HPO_2Cl_2$	41,8	5,4	28,5	7,5	8,3	84
IVe	157,5—160	367 (3,80)	723, 782, 1505, 1550, 1613, 2400—3070, 3100	56,9	7,3	26,0	10,1		$C_{13}H_{19}ClN_2 \cdot HCl$	56,7	7,3	25,8	10,2		95
Ve[a]		353 (3,48)	1552, 1620, 3000, 3070, 3200	64,5	7,5	13,3	11,3		$C_{13}H_{19}ClN_2$	65,4	8,0	14,9	11,7		98

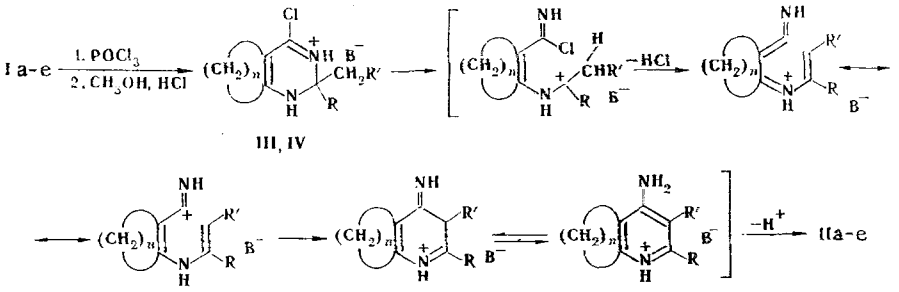
[a]Not an individual substance.

46-70% yields in inert solvents at 110°C (for III) and 170°C (for IVe). Recyclization does not occur at lower temperatures: the starting salts are recovered. The difference in the temperatures that are necessary for the recyclization of dichlorophosphoryl salts III and hydrochloride IVe is evidently due to the different ion pair interaction in the salts. The free bases were not obtained in analytically pure form because of their extremely facile oxidizability (admixed oxidation products were always detected). Recyclization does not occur when free bases V are heated in inert solvents, and only oxidation and destruction products are formed.

The ability of only 2,2-disubstituted 4-chloro-1,2-dihydropyrimidine salts to undergo recyclization to 4-aminopyridines and the absence of this ability in the case of the corresponding bases, as well as the effect of the polarity of the solvent on the rate of recyclization, indicate the cationotropic character of this reaction. Thus the recyclization of hexahydroquinazolone derivative Ie to 9-aminooctahydroacridine IIe under the influence of an equimolar amount of $POCl_3$ (in toluene at 110°C) proceeds at a rate that is six to seven times faster than the reaction in a tenfold excess of $POCl_3$ without a solvent at the same temperature.

Although intermediate salts III and IV were not isolated for 4-oxodihydropyrimidine derivatives Ib-d, it may be assumed that their recyclization to 4-aminopyridine derivatives proceeds similarly.

The results obtained in this study make it possible to propose the following mechanism for the recyclization of 2,2-disubstituted 4-chloro-1,2-dihydropyrimidine salts: 1) opening of the pyrimidine ring, under the influence of the temperature, at the C_2—N_3 bond, which is the most weakened by the positive charge, and the formation of a carbonium ion; 2) elimination of HCl with the formation of a new mesomeric cation; 3) intramolecular electrophilic attack with recyclization to 4-aminopyridine derivatives.



A comparison of the formally logical mechanisms of the previously observed [1] cationotropic rearrangement of 4-oxo-1,2-dihydropyrimidine derivatives I to 2-pyridones under the influence of polyphosphoric acid (PPA) and the rearrangement of 4-chloro-1,2-dihydropyrimidine derivatives III and IV to 4-aminopyridines II, which is described in the present communication, shows that the necessary conditions for the occurrence of both rearrangements are: 1) the formation of a protonated 1H,3H-pyrimidine cation; 2) the action of the high temperatures (110-170°C) that are necessary for cleavage of the N_1—C_2 or C_2—N_3 bond; 3) the absence of polar solvents that are capable of solvation. The difference in the final products of the rearrangements, i.e., the formation of primarily 2- or 4-substituted pyridines, is determined by the greater or smaller degree of localization of the positive charge on the N_1 or N_3 atom in the corresponding pyrimidine cation.

Thus the two recyclizations are different variants of the new intramolecular cationotropic rearrangement that is characteristic for 2,2-dialkyl-substituted 1,2-dihydropyrimidines that have a functional substituent such as an oxo or chloro substituent in the 4 position. In contrast to aromatic pyrimidine compounds, for which rearrangements under the influence of various nucleophilic agents are characteristic [6, 7], the investigated 1,2-dihydropyrimidines are stable in alkaline media but are inclined to undergo cationotropic recyclization to aromatic pyridine compounds.

EXPERIMENTAL

The UV spectra of solutions of the compounds in methanol were recorded with an SF-16 spectrophotometer. The IR spectra of KBr pellets were recorded with a UR-10 spectrometer. The PMR and ^{13}C NMR spectra were obtained with a Varian XL-100-12 spectrometer with tetramethylsilane as the internal standard.

4'-Chloro-1',2',5',6',7',8'-hexahydrospiro[cyclohexane-1,2'quinazoline] Dichlorophosphoryl Salt (IIIe). A 25-ml sample of $POCl_3$ was added to 3 g (13.5 mmole) of Ie, and the mixture was refluxed for 1 h. The yellow solution was poured into dry ether cooled to 0°C, and the yellowish precipitate was removed by filtration, washed on the filter with ether, and recrystallized from methanol–acetone–ether (1:20:20). The yield was 4.3 g (84%).

7-Chloro-2',3',4',5'-tetrahydrospiro[cyclohexane-1,5'-1'H-cyclopenta[d]-pyrimidine Dichlorophosphoryl Salt (IIIa). This compound was similarly obtained. The yield was 2.45 g (50%).

4'Chloro-1',2',5',6',7',8'-hexahydrospiro[cyclohexane-1,2'-quinazoline] Hydrochloride (IVe). A 3-g sample of salt IIIe was dissolved in methanol saturated with HCl, and hydrochloride IVe was precipitated with dry ether. The yellow precipitate was removed by filtration. The yield was 2.1 g (95%).

4'-Chloro-1',2',5',6',7',8'-hexahydrospiro[cyclohexane-1,2'-quinazoline] (Ve). Dichlorophosphoryl salt IIIe or hydrochloride salt IVe (1 g in each case) was dissolved in the minimum amount of alcohol, the resulting solution was made alkaline to pH 9-10 with ammonium hydroxide, and the white precipitate was removed by filtration and washed on the filter with water, acetone, and ether. The yield of base Ve was 0.63 g (97%) or 0.85 g (98%), respectively.

Rearrangement of Dichlorophosphoryl Salts IIIa, e and Hydrochloride IVe to 4-Aminopyridine Derivatives IIa, e. A solution of 1 g (2.68 mmole) of salt IIIe in 40 ml of toluene or a solution of 1 g (3.64 mmole) of salt IVe in 40 ml of o-dichlorobenzene was refluxed for 4 h, after which the organic layer was separated. The viscous brown residue was dissolved in 40 ml of aqueous methanol (1:1), the solution was made alkaline to pH 9-10 with ammonium hydroxide, and the precipitate was removed by filtration, washed on the filter with water, and dried to 40°C. The filtrate was extracted with chloroform (three 30-ml portions), and the chloroform was evaporated to give an additional amount of IIe. The yield of IIe from salt IIIe was 0.38 g (70%), while the yield of IIe from salt IVe was 0.45 g (61%). Recrystallization from methanol–water (1:5) gave a product with mp 222-224°C (mp 218-219°C [3]). The IR spectrum of IIe was similar to the IR spectra of IIa-d. The results of elementary analysis of IIe for C, H, and N were in agreement with the calculated values.

The rearrangement of salt IIIa was carried out by a method similar to that used to rearrange salt IIIe. The yield of IIa was 0.25 g (46%).

Rearrangement of 2,2-Disubstituted 4(3H)-Oxo-1,2-dihydropyrimidines Ia, b, d, e to 4-Aminopyridine Derivatives IIa, b, d, e under the Influence of an Equimolar Amount of $POCl_3$. A 0.03-mole of $POCl_3$ and 50 ml of dry toluene were added to 0.02 mole of Ia, b, d, e, and the mixture was refluxed for 2-5 h. The toluene layer was separated, and the viscous brown residue was dissolved in 40 ml of aqueous methanol (1:1), and the solution was made alkaline to pH 9-10. The precipitated IIa, b, d, e were removed by filtration, washed with water, and dried. Additional amounts of IIa, b, d, e were obtained from the chloroform extracts of the aqueous filtrates. The products (II), reaction times, and yields were as follows: IIa, 5 h, 52.6%; IIb, 3 h, 45%; IId, 3 h, 57.2%; IIe, 2 h, 92%. The IR spectra and melting points of IIa-d obtained by the described method and by the method in [2] were identical.

Rearrangement of 2,2-Disubstituted 4(3H)-Oxo-1,2-dihydropyrimidines Ia-e to 4-Aminopyridine Derivatives IIa-e under the Influence of Excess $POCl_3$ in Toluene. A 20-ml sample of $POCl_3$ and 50 ml of dry toluene were added to 0.02 mole of Ia-e, and the mixture was refluxed for 10-24 h until it darkened. The toluene layer was separated, and the viscous brown residue was dissolved in 40 ml of aqueous methanol (1:1). Compounds II were obtained as described above. The products (II), reaction times, and yields were as follows: IIa, 24 h, 79%, IIb, 14 h, 74%; IIc, 10 h, 38%; IId, 14 h, 84%; IIe, 14 h, 85%.

The characteristics of the newly synthesized substances are presented in Tables 1 and 2.

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NEW METHOD FOR THE SYNTHESIS OF SOME POLYFUNCTIONAL 5-AMINOPYRIMIDINES

R. G. Melik-Organdzhanyan, T. A. Khachaturyan, V. S. Mirzoyan, and F. G. Arsenyan

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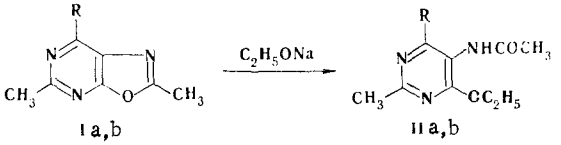
A preparative method for the synthesis of some 5-aminopyrimidines, which consists in the nucleophilic opening of the oxazole ring of 2,5-dimethyl-7-chloro- and 7-amino-substituted oxazole[5,4-d]pyrimidines under the influence of acids and bases, was developed.

5-Aminopyrimidines are the starting compounds for the synthesis of various condensed pyrimidines and are of interest as biologically active substances. The widely known methods for the preparation of compounds of this type are multistep processes and are based on starting compounds that are difficult to obtain [1].

Moreover, the lack of literature data on the stability of the oxazole ring in oxazolo[5, 4-d]pyrimidines compelled us to investigate its behavior in acidic and alkaline media in the case of the readily accessible 2,5-dimethyl-7-chloro- and 7-amino-substituted oxazolo[5, 4-d]-pyrimidines [2, 3].

In contrast to oxazoles, the majority of which are resistant to the action of acids and alkalis [4], the reaction of 2,5-dimethyl-7-chloro- and 7-amino-substituted oxazolo[5,4-d]-pyrimidines with sodium ethoxide leads to opening of the oxazole ring:



I a,b II a,b

I, II a R = Cl; b R = $N(C_2H_5)_2$

The hydrolysis of oxazolo[5,4-d]pyrimidines under the influence of acids proceeds just as readily. 2-Methyl-4-chloro-5-amino-6-hydroxypyrimidine hydrochloride (IIIa) was obtained in high yield by the action of hydrochloric acid on Ia in benzene or alcohol. 2-Methyl-4-chloro-5-acetamido-6-hydroxypyrimidine (IVa), which was deacetylated to give IIIa upon refluxing with hydrochloric acid, was formed when a weaker acid (such as acetic acid) was introduced into the reaction.

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