INTRAMOLECULAR REARRANGEMENT OF TWO-RING 2,2-DISUBSTITUTED 4-OXO-1,2,3,4-TETRAHYDROPYRIMIDINES UNDER THE INFLUENCE OF POLYPHOSPHORIC ACID

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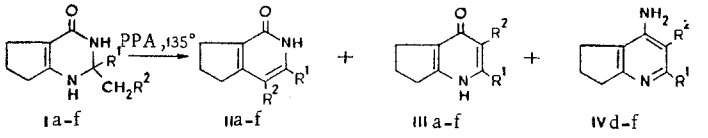
Intramolecular rearrangement of two-ring 2,3-disubstituted 4-oxo-1,2,3,4-tetrahydropyrimidines to pyridine derivatives, which takes place under the influence of polyphosphoric acid, was observed. It is shown that cycloalkanopyrimidones are converted primarily to two- or three-ring 2-pyridones and to small amounts of the corresponding 4-pyridones and 4-aminopyridines. A possible mechanism that enables one to explain the difference in the occurrence of the rearrangements primarily to 2- or 4-pyridones as a function of the absence or presence of aromatic character of the ring condensed with the pyrimidine ring is proposed.

During a study of the properties of the 5,5-disubstituted 7-oxo-1,2,3,4,6,7-hexahydrocyclopenta[d]pyrimidines (Ia-f) obtained in [1], which will subsequently for greater convenience be considered to be derivatives of 2,2-disubstituted 4-oxo-1,2,3,4-tetrahydropyrimidines, we observed that at 135 deg C in polyphosphoric acid (PPA) they are converted to compounds of the pyridine series. Thus two-ring 2,2-dialkyl-substituted 4-oxotetrahydropyrimidines Ia-c are converted to two-ring 2-pyridones IIa-c in 25-40% yields. Under the same conditions two-ring 4-oxotetrahydropyrimidines with spiran structures Id-f are converted to three-ring 2-pyridones IId-f in 60-72% yields.

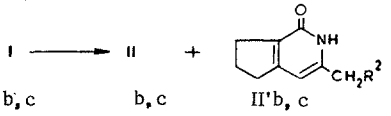


Ia-f IIa-f IIIa-f IVd-f

I-III a $R^1=CH_3, R^2=H$; b $R^1=R^2=CH_3$; c $R^1=CH_3, R^2=C_2H_5$

I-IV d $R^1+R^2=(CH_2)_3$; e $R^1+R^2=(CH_2)_4$; f $R^1+R^2=(CH_2)_5$

For 2,2-dialkyl-substituted pyrimidones Ib, c one might have proposed the formation of two isomeric 2-pyridones — IIb, c and II'b, c — as a result of rearrangement.



b, c b, c II'b, c

However, the PMR spectra of the isolated compounds confirm the completely substituted pyridone structures IIb, c (from the absence of signals of aromatic protons and the presence of signals of six methyl protons at 1.85 and 2.17 ppm for IIb and at 1.05 and 2.27 ppm for IIc).

The 2-pyridone structures IIa, b, d-f were previously established in [2]. The new compounds Ic and IIc were synthesized by the method in [1, 2].

In addition to 2-pyridones IIa-f, small amounts of 4-aminopyridine derivatives IVd-f with known structures [3] and 4-pyridone derivatives IIIa-f, the structures of which were proved by alternative synthesis by diazotization of the corresponding 4-aminopyridines and confirmed by the IR spectra, were isolated from the reaction mixture (Table 1). Characteristic strong absorption bands at 1490-1540 cm^{-1}, which can be assigned to $\nu_{C=O}$ and δ_{N-H}, are observed in the IR spectra of the 4-pyridones; the less intense band at 1625-1630 cm^{-1}

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TABLE 1. Results of the Rearrangement

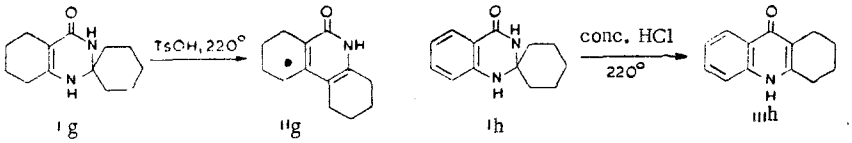
Starting compound	Yield of rearrangement products, %		
	II	III	IV
Ia	25	0,5	Traces*
Ib	40	1,0	Traces*
Ic	25	0,5	Traces*
Id	66	1,2	0,1
Ie	70	2,7	0,1
If	72	1,9	0,1 (10,8†)
Ig	96	Traces	0,5
Ih‡	—	54,4	—

*Traces are readily detected by means of TLC (bright-violet spots).
†This is the result of a single experiment.
‡According to the data in [5], rearrangement under the influence of concentrated HCl at 220 deg C.

is a ν_{ring} band [4]. A broad ν_{N-H} band of an associated group with several maxima is observed at 2400-3250 cm^{-1}.

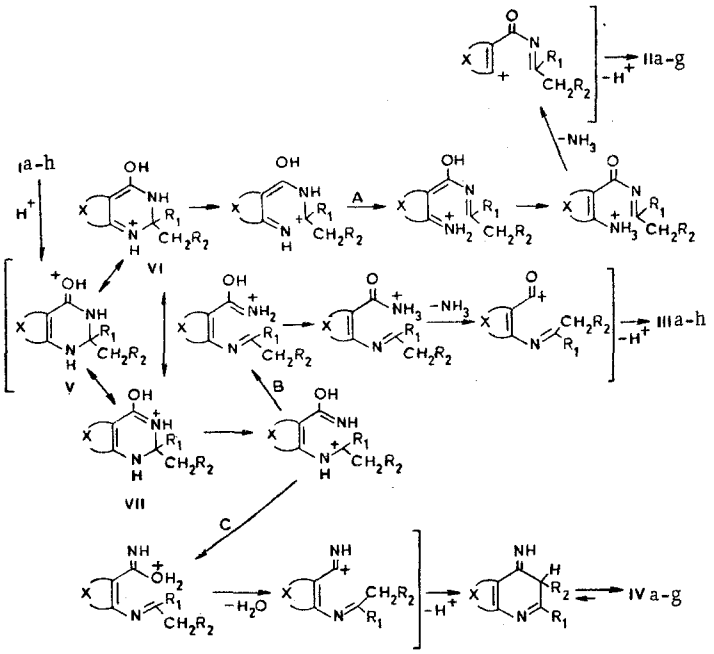
These sorts of conversions of the pyrimidine ring to a pyridine ring have not been previously described, although two instances of an analogous conversion for quinazolones with a spiran structure [5], which are also two-ring derivatives of 2,2-disubstituted 4-oxotetrahydropyrimidine, are known. Thus octahydroquinazolone Ig in the presence of concentrated HCl or p-toluenesulfonic acid (TsOH) at 220 deg C is converted to octahydrophenanthridone IIg, i.e., to a 2-pyridone derivative. It is interesting that under the same conditions tetrahydroquinazolone Ih is converted in good yield to tetrahydroacridone IIIh, which is a 4-pyridone derivative.

In an investigation of the conversion of octahydroquinazolone Ig to pyridone IIg we found that it is accomplished under milder conditions (at 135 deg C) and in 96% yield under the influence of PPA; in addition, 9-amino-1,2,3,4,5,6,7,8-octahydroacridine IVg, the structure of which is known [6], was isolated from the reaction mixture in 0.5% yield (Table 1).



Ig IIg Ih IIIh

Thus the conversion of pyrimidine compounds to pyridine compounds is characteristic for two-ring derivatives of 2,2-disubstituted 4-oxo-1,2,3,4-tetrahydropyrimidine, during which cycloalkanopyrimidones are converted primarily to the corresponding 2-pyridones and to very small amounts of 4-pyridones and 4-aminopyridines, while tetrahydropyrimidine condensed with an aromatic ring, i.e., tetrahydro-4-quinazolone, is converted primarily to a 4-pyridone derivative (Table 1). It should be noted that all of the transformations of this sort take place at high temperatures in strongly acidic media. This enabled us to assume that the observed conversion of 2,2-disubstituted 4-oxo-tetrahydropyrimidines Ia-h to pyridones IIa-g or IIIh is an intramolecular cationotropic rearrangement. Protonation of the oxygen atom to give the mesomeric cation VI ↔ V ↔ VII, the charge on which is delocalized between the oxygen and N_1 and N_3 atoms, evidently occurs in the first step of the reaction. This is followed by opening of the pyrimidine ring at the N_1-C_2 or C_2-N_3 bond as a function of the size of the contribution of canonical structures VI and VII to the hybrid structure of protonated pyrimidone. Subsequent prototropic transformations of the A, B, or C types and splitting out of ammonia or water lead to 2-pyridone derivatives II, 4-pyridone derivatives III, and 4-aminopyridine derivatives IV. The proposed mechanism makes it possible to explain the difference in the occurrence of the rearrangement primarily to 2- or 4-



pyridones in the case of 2,2-disubstituted 4-oxotetrahydropyrimidines condensed with a cycloalkane or an aromatic benzene ring. Thus structures V and VI make a significant contribution to the mesomeric cation in the protonation of cycloalkanopyrimidones Ia-g, since in this case the degree of delocalization of the positive charge is greater than in the case of participation of canonical structure VII; the N_1-C_2 bond therefore undergoes cleavage readily, and primarily 2-pyridone derivatives IIa-g are formed, along with only small amounts of 4-pyridone derivatives IIIa-f and 4-aminopyridine derivatives IVd-g. On the other hand, structure VII makes a significant contribution to the stabilization of protonated 4-oxo-1,2,3,4-tetrahydroquinazolone Ih, since structure VI, which is associated with disruption of the aromaticity, is less favorable; ring cleavage therefore occurs at the C_2-N_3 bond, and the principal rearrangement product is 4-pyridone derivative IIIh.

Only a slight degree of rearrangement occurs when Ia-g are heated in aqueous solutions of HCl or H_3PO_4; the principal process is hydrolysis with disruption of the pyrimidine ring to give ketones and the products of their self-condensation, i.e., in aqueous solutions of acids nucleophilic attack on the carbonium ions by water molecules turns out to be preferable to intramolecular rearrangement.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. The UV spectra of methanol solutions of the compounds were recorded with an SF-4A spectrophotometer. The PMR spectra of deuteroethanol solutions of the compounds were recorded with a Hitachi–Perkin–Elmer R-20 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The individuality of the compounds obtained was monitored by thin-layer chromatography (TLC) on activity II aluminum oxide in a benzene–methanol system (92 : 8). Preparative TLC was carried out under the same conditions. The chromatograms were developed in iodine vapors.

5-Methyl-5-propyl-7-oxo-1,2,3,4,6,7-hexahydrocyclopenta[d]pyrimidine (Ic). A mixture of 6 g (0.0555 mole) of 1-amino-2-cyanocyclo-1-pentene, 7.3 g (0.084 mole) of methyl propyl ketone, 60 g of PPA, and 60 ml of dry benzene was stirred at 80 deg C for 3 h, after which 60 ml of cold water was added with stirring. The benzene layer was separated and discarded. The aqueous layer was extracted with five 30-ml portions of chloroform, and the chloroform extract was also discarded. The aqueous layer was neutralized to pH 6-7 with 22% ammonium hydroxide, and the resulting precipitate was washed successively on the filter with water and acetone. It was recrystallized from methanol–water (5 : 1) to give 7.67 g (71%) of Ic.

3-Methyl-4-ethyl-1-oxo-1,2,3,4-tetrahydro-5H-2-pyridine (IIc). This compound, with mp 135-140 deg C, was synthesized by the method in [2]. The molar ratio of 1-amino-2-cyanocyclo-1-pentene, methyl propyl ketone, and PPA was 1 : 1.3 : 10. The reaction time was 3 h. The product was recrystallized from methanol–water (5 : 1).

TABLE 2. Characteristics of the Synthesized Compounds

Compound	mp, °C	Found, %			Empirical formula	Calc., %			UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}	Yield, %
		C	H	N		C	H	N			
IIIb	348—350*	73,7	8,1	8,8	$C_{10}H_{13}NO$	73,6	8,0	8,6	265 (4,24)	1500—1553, 1626, 2500—3000, 3045, 3227	66
IIId	398—400*	75,4	7,6	7,8	$C_{11}H_{13}NO$	75,4	7,5	8,0	265 (4,27)	1500—1555, 1628, 2500—3000, 3025, 3200	80
IIIe	382—384*	76,0	8,0	7,4	$C_{12}H_{15}NO$	76,2	7,9	7,4	267 (4,23)	1490—1542, 1625, 2400—3000, 3050, 3240	64
IIIf	363—365*	76,7	8,2	7,1	$C_{13}H_{17}NO$	76,8	8,4	6,9	268 (4,24)	1478—1545, 1628, 2400—3000, 3045, 3240	80
Ic	174—176	68,0	9,2	14,2	$C_{11}H_{18}N_2O$	68,0	9,3	14,4	308 (3,78)	1550, 1560, 1605—1630, 3070, 3210	71
IIc	218—220	74,5	8,5	7,9	$C_{11}H_{15}NO$	74,6	8,5	7,9	238 (3,80) 307 (3,91)	1565, 1650, 2400—3200	43

*With decomposition. Prior to melting, this compound undergoes partial sublimation.

Rearrangement of 2,2-Disubstituted 4-Oxo-1,2,3,4-tetrahydropyrimidines to Pyridine Derivatives. A 5-g sample of the starting 2,2-disubstituted 4-oxotetrahydropyrimidine (Ia-g) was added to heated (to 80 deg C) PPA (a tenfold excess), and the mixture was heated at 135-140 deg C for 3 h. It was then cooled and diluted with a fivefold volume of water, and the aqueous mixture was extracted with ether to remove the decomposition products without amine character. The ether extract was discarded. The aqueous layer was neutralized with 22% ammonium hydroxide to pH 7, and the precipitated 2-pyridone (IIb-g) was removed by filtration and washed with water and acetone (Compound IIa did not precipitate; it was obtained from the chloroform extract of the neutral aqueous layer.). The neutral aqueous layer was extracted with three 40-ml portions of chloroform. The solid residue remaining after removal of the chloroform and washing with ether was a 4-pyridone or a mixture of 2-pyridone and 4-pyridone; the mixture was separated by preparative TLC. The aqueous layer was made alkaline to pH 10 with concentrated NH_4OH and extracted with five 40-ml portions of chloroform. The residue after removal of the chloroform was washed with ether. The residual solid was a 4-pyridone or 4-aminopyridine or a mixture of these two substances; the mixture was separated by preparative TLC. The yields (based on the crude reaction products) are presented in Table 1.

Alternative Synthesis of 4-Oxopyridines (IIIb, d-f). A solution of sodium nitrite in 10 ml of water was added in small portions at 20 deg C to a solution of 0.004 mole of 4-aminopyridine in 20 ml of 10% sulfuric acid, and the mixture was heated on a boiling-water bath for 30 min. It was then cooled and neutralized to pH 7 with dilute NH_4OH. The precipitated 4-oxopyridine was removed by filtration, washed with water and acetone, and crystallized from methanol.

The yields and characteristics of the newly synthesized substances are presented in Table 2.

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