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CYCLOCONDENSATION OF 4-HYDROXY-5,6-DIAMINOPYRIMIDINE WITH α,β-DIHALOCHALCONES

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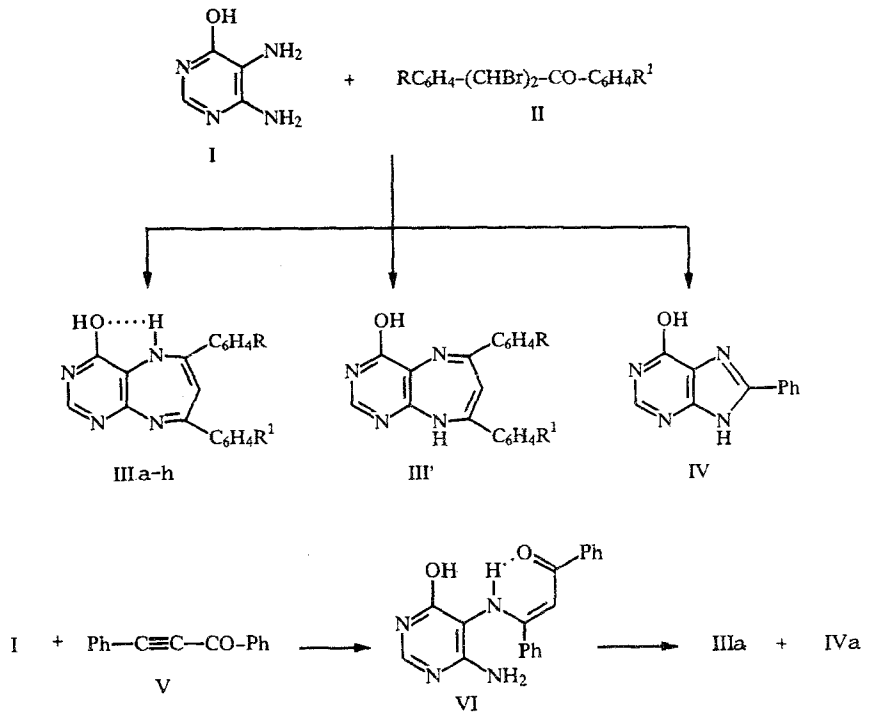
The condensation of 4-hydroxy-5,6-diaminopyrimidine with 1,3-diaryl-2,3-dihalopropanones and with dibenzoylacetylenes was used to obtain derivatives of 1H-pyrimido[4,5-b]-1,5-diazepine and pyrimido[4,5-b]pyrazine, respectively. Their spectral characteristics were studied, and the directions in the formation of 7- and 6-membered heterocycles were determined. The synthesized pyrimido[4,5-b]pyrazines exist in the form of two tautomeric species — enaminocarbinol and enol forms, with an intramolecular hydrogen bond of the chelate type.

In this article we will present results of an investigation of the interaction of 4-hydroxy-5,6-diaminopyrimidine (I) with the ketones IIa-h and other aromatic ketones (V-XII). We had shown previously [1] that 5,6-diamino-1,3-dimethyluracil with 1,3-diaryl-2,3-dibromopropanones II forms β-hetarylaminochalcones, extended boiling of which leads to derivatives of pyrimido[4,5-b]azepine.

The reaction of the diamine I with the dibromides IIa-h was performed analogously, but the boiling time in this case was reduced to 1-1.5 h, reflecting the higher reactivity of the diamine I in comparison with 5,6-diamino-1,3-dimethyluracil. From the reaction mixture, compounds IIIa-h were recovered with yields of 42-63%; according to elemental analyses and spectroscopic data, these are 2,4-diaryl-8-hydroxy-1H-pyrimido[4,5-b]-1,5-diazepines.



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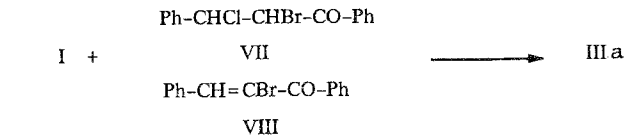
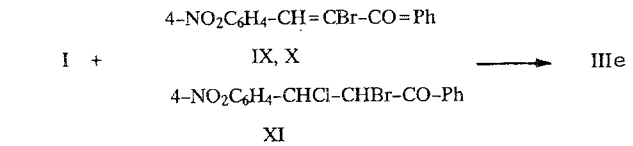
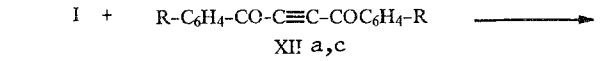


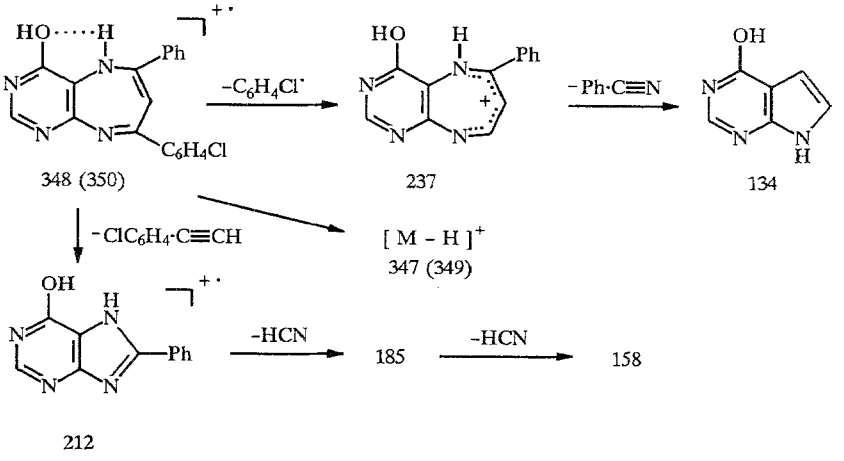




XIII a,c

II, III, XI, XIII a-c R^1 = H; a R = H, b R = OCH_3, c R = Cl, d R = Br, e R = NO_2;
f R^1 = OCH_3, R = NO_2; g: R^1 = Cl, R = NO_2; R^1 = Br, R = NO_2

The mass spectra of compounds IIIa-c,e contain peaks of the respective molecular ions. The fragmentation processes follow a common path, which is shown below in the example of fragmentation of compound IIIc:



In the IR spectra of compounds IIIa-h, bands of $\nu_{C=C}$ are manifested; these are sensitive to the electronic influence of the substituent R that has been introduced (Table 1). A complex spectral pattern is observed in the 3200-3500 cm^{-1} region, where two and sometimes three bands can be observed, assigned to stretching vibrations of free and bound NH and OH groups.

In the PMR spectra of compounds IIIa,d,e, two singlets are distinguished, corresponding to protons of the =CH group of the pyrimidine and diazepine rings, and also a multiplet of aromatic protons at 7.56-8.22 ppm. A feature of these spectra is the absence of any signals in the 11-12 ppm region, where the signal of the OH group in position 4 of the pyrimidine ring is usually manifested. Such a signal is observed, for example, in the PMR spectra of 2,3-dihydropyrimido[4,5-b]diazepines, azomethines, or purines synthesized from the diamine I and chalcones or aromatic aldehydes [2]. Along with the other signals in the spectra of compounds IIIa,d,e, there is a broadened signal at 7.2-7.3 ppm, equal in integral intensity to two protons; this

TABLE 1. Characteristics of Synthesized Compounds

Compound	mp, °C	UV spectra, λ_{max}, nm (and $\varepsilon \cdot 10^{-3}$	IR spectra		R_f ($CHCl_3$)	Yield, %
			$\nu_{C=C}$	ν_{NH} (ν_{OH})		
IIIa	220...222	279(14,6), 302(11,7), 400(9,1)	1632	3286, 3460	0,50	42
IIIb	232...233	241(14,6), 281(16.4), 303(18,1), 400(13,2)	1645	3223, 3283, 3480	0,56	49
IIIc	259	283(14,6), 300(17,3), 401(12,6)	1648	3293, 3452	0,51	57
IIId	260...261	245(19,2), 283(16,8), 306(19,2), 400(13,6)	1645	3229, 3286, 3463	0,54	63
IIIe	285...286	257(15,7), 329(11,5), 412(16,7)	1662	3253, 3303, 3403	0,52	62
IIIf	268	260(14,0), 342(16,8), 411(12,7)	1652	3292, 3310, 3412	0,57	56
IIIg	296...297	253(16,1), 329(11,0), 412(14,6)	1662	3249, 3340, 3480	0,53	60
IIIh	297...298	256(3,9), 329(11,2), 408(14,9)	1660	3245, 3325, 3477	0,55	53
VI	173...174	253(11,8), 346(14,4),	1630	3316, 3400	0,05	65
XIIIa	279	246(20,0), 343(13,5)	1605 1696*	—	—	81
XIIIc	319...320	256(16,2), 348(12,6), 417(8,1)	1605, 1692*	—	—	72

*These are values of $\nu_{C=O}$.

signal should be assigned to resonance absorption of protons of the OH and NH groups, experiencing rapid exchange. The most probable source of such exchange is an intramolecular hydrogen bond with the participation of these groups.

In the UV spectra, three rather intense absorption bands are manifested in the 280-413 nm region. A slight bathochromic shift of the long-wave absorption band is observed upon introducing the strongly electron-accepting nitro group into the p-position of the 2-aryl substituent (compounds IIIg-h).

In a number of experiments in the reaction of the diamine I with the ketone IIa, 4-hydroxy-8-phenylpurine (IVa) was recovered, with its yield increasing as the boiling time of the reaction mixture was extended. Its structure was confirmed by counter-synthesis (reaction of 4-hydroxy-5,6-diaminopyrimidine with benzaldehyde in the presence of N-bromosuccinimide [2]), and also by its spectral characteristics (IR and UV).

We also introduced into reaction with the diamine I the compounds 1,3-diphenylpropyn-3-one (V), 1,3-diphenyl-2-bromo-3-chloropropanone (VII), α-bromochalcone (VIII), and the corresponding nitro derivatives of the haloketones (IX, X, and XI). Interaction of the diamine I with compound V affords a compound with a bright yellow color (VI), mp 174°C, which, upon boiling in alcohol with catalytic additions of AcOH for 10-12 h, forms a mixture of the pyrimidodiazepine (IIIa) and the purine (IVa) (monitored by TLC and UV spectroscopy); this suggests the enaminoketone structure for compound VI. This view is consistent with its spectral characteristics. Thus, in the PMR spectrum we observe a series of signals with chemical shifts 6.05, 6.79, and 7.65 ppm, which are assigned on the basis of position and integral intensity to resonance absorption of the proton of the CH group at the multiple bond, protons of the amino group in position 6, and the proton of the pyrimidine ring, respectively. The signal at 11.52 ppm can be assigned to the proton of the OH group of the pyrimidine ring. But since this signal corresponds to two protons in integral intensity, it appears probable that, as a consequence of rapid exchange, the signal of the proton of the chelated NH group falls into this same region. In the IR spectra of compound VI, we observe absorption bands at 1607 cm^{-1} ($\nu_{C=C}$) and 1630 cm^{-1} ($\nu_{C=O}$); the lowered value of $\nu_{C=O}$ is characteristic for enaminoketones and is due to the existence of an intramolecular hydrogen bond [3]. In the 3300-3400 cm^{-1} region we have identified unambiguously certain bands of symmetric and asymmetric vibrations of the primary amino group. Also characteristic is the hypsochromic shift of the long-wave absorption band of the enaminoketone VI in comparison with the band in the spectra of compounds IIIa-h (Table 1). The proposed structure of compound VI is also consistent with its mass spectrum, in which the molecular ion with m/z 332 undergoes fragmentation in two directions: detachment of the aroyl radical to form an ion with m/z 227, and elimina-

TABLE 2. Mass Spectra of Certain Synthesized Compounds

Compound	m/z (and intensity, in %)*
III	314(100), 313(18), 238(5), 237(12), 236(8), 213(8), 212(6), 211(5), 189(31), 165(7), 89(11)
III	350(35), 349(38), 348(100), 237(58), 236(27), 225(35), 189(37), 89(31)
III	359(16), 257(24), 224(20), 225(100), 222(5), 212(7), 137(14), 122(98), 110(54), 89(10)
VI	332(12), 314(43), 227(19), 227(19), 212(38), 183(6), 120(10), 105(100), 77(72)
XIII	412(4), 410(7), 393(8), 274(9), 273(6), 271(25), 236(8), 141(30), 140(9), 139(100), 138(5), 113(10), 111(31), 91(5)

*Peaks of molecular ions are underlined. Peaks with intensity $\geq 5\%$ are listed here.

tion of a water molecule to form a pyrimidodiazepine structure. The subsequent decomposition is completely consistent with the fragmentation of compound IIIa.

The mechanism of the interaction of aromatic o-diamines with chalcone dibromide has been discussed in detail in [4]; the mechanism includes a debromination stage. At the same time, we noted in [2] certain cases of direct amination of chalcone dibromides when there is an electron-accepting substituent in their β-aromatic ring. In the reaction we have studied here, the interaction proceeds through a stage of elimination of the hydrogen halide. Evidence supporting this view may be found in the results of experiments with cis- and trans-p-nitro-α-bromochalcones (IX, X). In both of these experiments, we observed the formation of compound IIIe; in the case of the trans-α-bromo-p-nitrochalcone (VIII), the reaction was completed in 15 min, whereas in the case of the cis-isomer (IX), precipitation of solid material was observed only after 50 min. Such a difference in reactivity can be explained by differences in the rates of addition and elimination for the cis- and trans-isomers. The interaction of the diamine I with the ketones VII, VIII, and VI proceeds quite smoothly and with satisfactory yields. These results provide convincing evidence in favor of a mechanism that includes a stage of elimination, with the formation of an intermediate α-bromochalcone.

With regard to which direction is taken by the interaction of the diamine I with the dibromides IIa-h, we resolved this question in favor of a cyclic structure of the type of III (not the alternate III'), on the basis of the following considerations.

It is known [5] that the reactivities of amino groups in even-numbered positions of the pyrimidine ring are not consistent with their basicity constants. The most reactive is the 5-amino group, whereas the 6-amino group tends toward amine–imine tautomerism. Consequently, the 5-NH_2 group participates in reactions of nucleophilic addition at the double bond of the α-bromochalcone. This is consistent with the above-noted fact of intramolecular hydrogen bonding between the OH and N–H groups in compounds IIIa-h.

We also carried out reactions of the diamine I with polyelectrophilic ketones of the type of dibenzoylacetylene XIIa,c. After 2 h of boiling an alcohol solution with equimolar quantities of compounds I and XIIa,c, we recovered from the reaction mixture the compounds XIIIa,c, which were identified as 2-(4-R-phenacylidene)-3-(4-aryl)-8-hydroxy-1,2-dihydropyrimidino[4,5-b]pyrazines. The choice of the indicated structure was made on the basis of PMR spectra, which included unambiguous manifestations of a signal of the ethylene-bond proton with shifts of 6.43 and 6.30 ppm in compounds XIIIa,c respectively, as well as a signal of the pyrimidine ring proton at 8.34 ppm, and signals of hydroxyl group protons at 13.01 and 13.00 ppm. In the spectra of compounds XIIIa,c, in addition, we observed signals at 15.33 and 15.35 ppm, which were assigned to protons of the chelate ring of the tautomers A and B that are represented (see Scheme).

Such an assignment is in accord with literature data concerning structures that are capable of forming chelate tautomers [6]. In the IR spectra of compounds XIIIa,c, we observed bands in the 1595-1605 region (superposition of bands of $\nu_{C=C_{arom}}$ and $\nu_{C=N}$) and in the 1692-1696 cm^{-1} region ($\nu_{C=O}$). The vibrations of free bonds O–H and N–H, which we can expect in the case of nonchelate OH or NH tautomers, were not observed. Thus, from the PMR and IR spectroscopic data we can conclude that there are no nonchelate tautomers for compounds XIIIa,c.

The position of λ_{max} in the UV spectra of compounds XIIIa,c suggests the predominance of tautomer A, since the conjugation chain is larger in this tautomer than in B. In addition, the insignificant enolizability observed for other compounds that are similar in structure [6] provides further evidence in favor of predominance of the enamine tautomer.

The mass spectrometric decomposition of compound XIIIa includes splitting out aroyl and chlorophenyl radicals, with subsequent breakdown of the pteridine ring and the formation of fragment ions (Table 2).

The fact that the formation of 1,2-dihydropteridines is actually realized in the reaction of the diamine I with dibenzoylacetylenes, rather than the formation of pyrimido[4,5-b]diazepines, is a consequence of the greater thermodynamic favorability of the six-membered heterocycle in comparison with the seven-membered compound.

EXPERIMENTAL

The IR spectra were taken in a Specord IR-75 instrument in KBr tablets. The electronic spectra (in ethanol) were obtained in a Specord UV-Vis instrument. The PMR spectra were recorded in Bruker WP-360 and Varian KL-100 instruments in DMSO-d_6, with TMS internal standard.

The results of elementary analyses for N content matched the calculated values.

2,4-Diphenyl-8-1H-pyrimido[4,5-b]-1,5-diazepine (IIIa). To a solution of 0.30 g (2.7 mmoles) of the diamine I in 40 ml of methanol (or ethanol), 1.0 g (2.7 mmoles) of the ketone IIa and 2 ml of triethylamine were added; the mixture was refluxed for 2 h. The solvent was evaporated down to 1/2 volume, and the resulting precipitate was washed with hot water and crystallized from methanol. Yield 0.32 g. Compounds IIIb-h were synthesized analogously. The interaction of the diamine with the ketones VII, VIII, and XI was carried out analogously, with respective refluxing times 2.5, 1, and 1.5 h. Yields 24, 50 (IIIa), and 43% (IIIe), respectively.

β-(4-Hydroxy-6-amino-5-iminopyrimidine)chalcone (VI). A mixture of 0.22 g (2 mmoles) of the diamine I, 0.41 g (2 mmoles) of compound V, and 1 ml of acetic acid in 40 ml of 2-propanol was refluxed for 4 h. The precipitate was filtered off, washed with hot water, and crystallized from a 1:1 mixture of 2-propanol and DMF. Yield 0.4 g.

2-Phenacylidene-3-phenyl-8-hydroxy-1,2-dihydropyrimido[4,5-b]pyrazine (XIIIa). A mixture of 0.22 g (2 mmoles) of compound I, 0.47 g (2 mmoles) of dibenzoylacetylene, 1 ml of acetic acid, and 30 ml of methanol was refluxed for 2 h. After cooling and filtering, the product was crystallized from a 1:2 mixture of methanol and benzene. Yield 0.54 g.

Conversion of compound VI. A mixture of 0.33 g (1 mmole) of compound VI and 5 drops of acetic acid in 10 ml of ethanol was refluxed for 12 h. The bright-yellow residue dissolved. After cooling, the luminescing compound IIIa precipitated out, with an admixture of the purine IVa. After recrystallization from a 1:1 mixture of ethanol and chloroform, obtained 0.16 g of the diazepine IIIa. The filtrate was evaporated down to 1/3 volume, recovering 0.07 g of compound IVa.

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