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REACTIONS OF 5,6-DIAMINO-1,3-DIMETHYLURACIL WITH CARBONYL COMPOUNDS

V. D. Orlov and I. Z. Papiashvili

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The first step in the acid-catalyzed reaction of 5,6-diamino-1,3-dimethyluracil with carbonyl compounds is the formation of an azomethine at the 5-amino group. Chalcone derivatives undergo a further substitution; the 6-amino group is replaced by a hydroxyl group with subsequent ring closure and the formation of a 2,3-dihydro-1,5-oxazepine ring. Azomethines based on arylidenacetones forms 2,3-dihydropyrimidino[5,6-b]-1,5-diazepine derivatives.

In earlier work [1] we found that derivatives of pyrimidinohydrooxazepine, theophylline, and pyrimidinodihydrodiazepine can be prepared by the reaction of 5,6-diamino-1,3-dimethyluracil (I) with aromatic α,β-unsaturated ketones. The aim of the present work is to study the effect of a number of factors (catalyst, temperature, nature of carbonyl component) on these reactions.

The first experiments involved the reaction of the diamine (I) with chalcones using 1-2 drops of acetic or concentrated hydrochloric acid as catalyst [1]. In the present work it was shown that if the diamine I monohydrochloride was used in place of diamine (I) the yield of the product, dihydropyrimidinooxazepines (VII), increased by 10-20% and reached 90-97%. On the other hand, if the catalytic acid content was reduced to 1-5 mg (calculated for 1 mmole of reagent), two products were formed. Colorless crystals of a derivative of dihydropyrimidinoxazepine VII were first to separate from the hot reaction solution; on cooling the solution, yellow crystals of a second product (II) form along with the colorless crystals. If the filtrate is diluted with water, a mixture of products II and VII separates. An analogous result is achieved by carrying out the reaction at room temperature or at 0°, but in this case the time required to complete the reaction is increased to 3-4 days. Formation of a mixture of compounds IIa and VIIa is observed if the reaction of chalcone with the diamine is catalyzed by 1-5 mg of sulfuric acid of HBF_4; for example, when one drop of 3% HBF_4 was added per 10 ml of reaction mixture containing 1 mmole of reagents.

It was not possible to separate the products II and VII by the usual method of crystallization because during purification the yellow product II was converted to the corresponding compound VII; separation of the mixture of these products by crystallization from absolute methanol was ineffective. Pure yellow material could be isolated mechanically (i.e., by Pasteur's method of sorting crystals under a magnifying glass). This method is laborious and was used only to obtain pure compound IIa — the product of the reaction of chalcone with the diamine I. The IR spectrum of compound IIa contained a sharp doublet at 3415 and 3315 cm^{-1} due to the amino group. A characteristic feature of the UV absorption spectrum of IIa is a strong absorption band with λ_{max} 362 nm. These results, together with the elemental analysis (Table 1), suggest that compound IIa is an azomethine.

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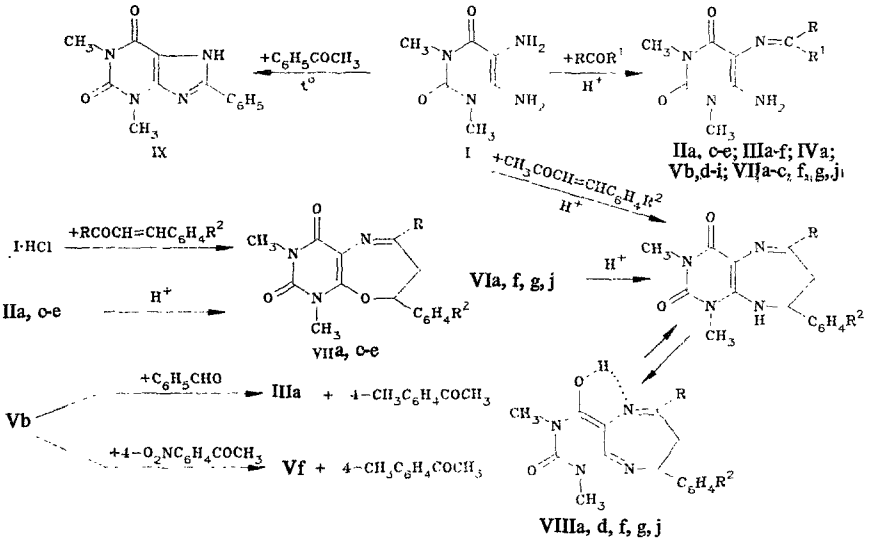
Formation of a mixture of compounds (IIc-e and VIIc-e) was also observed when other chalcones were allowed to react with the diamine I. The UV spectra of these mixtures contained long-wave absorption bands at 308-320 nm [1] from dihydropyrimidinooxazepine VII, and also absorption bands due to azomethines II (357-365 nm, Table 1). The IR spectra of all the mixtures contained doublets attributable to the νNH_2 group in compounds IIc-e (Table 1). On further heating, solutions of these mixtures form compounds VIIc-e, the properties of which are reported in [1]. The only possible interpretation of the observed data is that the yellow compounds II are themselves azomethines, formed from the 5-amino group of the diamine I.



II R=C_6H_5; III, IVa R=H; V, VI R=CH_3; II, VI R^1=CH=CH—$C_6H_4R^2$; III, V R^1=$C_6H_4R^2$; IVa R^1=CH=CH—C_6H_5; II—VI a R^2=H, b R^2=4-CH_3, c R^2=4-OCH_3, d R^2=4Cl, e R^2=4-Br, f R^2=4-NO_2, g R^2=3-NO_2, h R^2=2-OH, i R^2=2-OH—5-NO_2, j R^2=4-C_6H_5

A similar reaction of the diamine I with aromatic aldehydes is known [2]; a number of such azomethines (IIIa-f) are given in Table 1. We showed that the azomethine IVa is the only product of the reaction of cinnamic aldehyde with the diamine I; its spectral characteristics agree well with those of compound II (Table 1), thus confirming the proposed structure given above.

The preparation of the azomethine Vb from the reaction of p-methylacetophenone with the diamine I has been reported [3]. This synthesis has been repeated to give the azomethine Vb, the melting point of which is 26° higher than that reported in [3]. Our study also showed that acetophenone itself, and acetophenone derivatives containing electron-donor groups [4-OCH_3, 4-OH, 4-$N(CH_3)_2$], do not react with the diamine I in alcoholic solution.* On the other hand, acetophenones with electron-acceptor groups or an o-hydroxy group form the azomethine V in good yield. Heating an acidified alcoholic solution of the azomethine Vb and benzaldehyde or p-nitroacetophenone gives methylacetophenone or the azomethine IIIa or Vf, respectively. The synthesis of the azomethines is an equilibrium process, and the yield of products is largely determined by their thermodynamic stability. The introduction of an electron-acceptor substituent into the arylidene group of the azomethine (compounds Vd-g), or intramolecular hydrogen bond formation (compounds Vh and i) favor such a stabilization.

This also explains the results of the study of the reaction of the diamine I with arylideneacetones. The reaction of the arylideneacetones with electron-donor substituents (4-CH_3, 4-OCH_3) in the aromatic ring with the diamine I, carried out at 5-10° in the presence of a trace amount of acid, gives the azomethines VIb and c. On long standing, the reaction mixture becomes resinous. Similarly, benzylideneacetone and its 4-phenyl derivative give the azomethines VIa and j. If the reaction is carried out at room temperature, the compounds VIIIa and j (and VIIId) are formed; these differ in spectral characteristics from the azomethines VIa and j, but elemental analysis indicates that they are

*Boiling the diamine I with acetophenone gives 8-phenyltheophylline (IX).

TABLE 1. Characteristics of Azomethines II-VI

Compound*	mp, deg C	Reaction time, h	IR spectra (in KBr)		UV spectra in methanol, λ_{max}, nm ($\epsilon \cdot 10^{-3}$)	Found N, %	Empirical formula	Calculated N, %	Yield, %
			νNH_2	$\nu C=O$					
IIa	>300	0,2	3415, 3315	1689	362 (8,7), 250 (14,3)	15,4	$C_{21}H_{20}N_4O_2$	15,5	—
IIc	—	0,3	3410, 3312	1692	357, 275	—	$C_{22}H_{22}N_4O_2$	—	—
IId	—	0,2	3422, 3320	1690	363, 266	—	$C_{21}H_{19}ClN_4O_2$	—	—
IIe	—	0,2	3424, 3320	1690	365, 272	—	$C_{21}H_{19}BrN_4O_2$	—	—
IIIa	224—225 (225 [2])	1,0	3409, 3289	1695	343 (20,0), 289 (16,1), 238 sh , 226 (11,3)	21,7	$C_{13}H_{14}N_4O_2$	21,6	89
IIIb	233—234 (233 [2])	1,5	3395, 3295	1695	344 (25,0), 332 sh, 291 (17,2), 241 (9,3), 234 (11,1)	20,0	$C_{14}H_{16}N_4O_2$	20,6	69
IIIc	205—206 (206 [2])	2,0	3422, 3322	1690	346 (28,4), 333 sh , 292 (20,0), 204 sh , 232 sh	19,2	$C_{14}H_{16}N_4O_3$	19,4	64
IIId	219—220 (220 [2])	1,0	3415, 3318	1702	351 (25,5), 288 (17,1), 240 (14,0)	19,0	$C_{13}H_{13}ClN_4O_2$	19,1	92
IIIe	222—223	1,0	3422, 3322	1700	358 (18,2), 287 (8,7), 233 (21,8)	16,6	$C_{13}H_{13}BrN_4O_2$	16,6	90
IIIf	315—316	0,5	3455, 3355	1702	410 (21,2), 287 (15,4), 252 sh	23,0	$C_{13}H_{13}N_5O_2$	23,1	89
IVa	276—277	1,0	3415, 3295	1695	367 (31,1), 293 (19,3), 226 sh	19,5	$C_{15}H_{16}N_4O_2$	19,7	76
Vb	247—248 (221 [3])	3,5	3397, 3296	1680	355 (6,1), 284 sh, 258 (21,7)	19,4	$C_{15}H_{18}N_4O_2$	19,6	54
Vd	244—245	1,4	3388, 3288	1685	364 (5,7), 286 sh, 256 (21,9)	18,3	$C_{14}H_{15}ClN_4O_2$	18,3	70
Ve	236—237	1,5	3415, 3282	1689	366 (6,3), 285 sh, 259 (23,4)	15,6	$C_{14}H_{15}BrN_4O_2$	15,9	64
Vf	251—252	1,0	3402, 3309	1695	418 (6,3), 277 (26,8)	22,2	$C_{14}H_{15}N_5O_4$	22,1	80
Vg	227—228	1,0	3422, 3335	1702	368 (5,3), 280 (22,1), 254 (25,3), 229 (29,9)	22,3	$C_{14}H_{15}N_5O_4$	22,1	73
Vh	292—293	1,0	3389, 3322	1695	362 (6,7), 283 (15,5), 267 (17,1), 268 (16,2)	19,2	$C_{14}H_{16}N_4O_3$	19,4	68
Vi	247—248	0,5	3396, 3382	1689	382 (8,6), 319 (11,7), 277 sh, 263 (22,4), 227 (21,9)	21,2	$C_{14}H_{15}N_5O_5$	21,1	61
VIa	>300	0,1	3430, 3312	1696	355 (9,6), 270 (11,2)	19,4	$C_{16}H_{18}N_4O_2$	19,4	60
VIb	>300	0,2	3428, 3322	1698	350 (10,5), 267 (11,5), 230 (17,9)	18,0	$C_{17}H_{20}N_4O_2$	18,0	58
VIc	>300	0,3	3420, 3300	1698	348 (8,7), 269 (11,3), 227 (18,2)	17,1	$C_{17}H_{20}N_4O_2$	17,1	50
VIf	>300	0,1	3415, 3322	1692	462 (7,9), 284 (18,5)	20,4	$C_{16}H_{17}N_5O_4$	20,4	89
VIg	>300	0,2	3415, 3310	1686	360 (6,2), 279 (19,8)	20,4	$C_{16}H_{17}N_5O_4$	20,4	83
VIj	>300	0,3	3429, 3315	1691	385 (11,2), 280 (12,0)	14,9	$C_{22}H_{22}N_4O_2$	15,0	45

*Compounds IIc-e in mixtures with dihydropyrimidinooxazepines VIIc-e, respectively.

TABLE 2. 4,7,9-Trimethyl-2-(4-R-phenyl)-6-hydroxy-8-oxo-2,3-dihydropyrimidino[5,6-b]-1,5-diazepines (VIII)

Compound	mp, deg C	Reaction time	IR spectrum (in KBr)		UV spectrum (in methanol)	Found N, %	Empirical formula	Calc. N, %	Yield, %
			νOH	νC=O	λmax, nm (ε·10⁻³)				
VIIIa	165—166	10	3403	1699	272 (9,8)	18,6	$C_{16}H_{18}N_4O_2$	18,8	52
VIIId	203—204	16	3416	1699	269 (14,2)	16,9	$C_{16}H_{17}ClN_4O_2$	16,8	54
VIIIf	220—221	30	3429	1701	274 (22,3)	20,2	$C_{16}H_{17}N_5O_4$	20,4	57
VIIIg	213—214	30	3415	1699	260 (17,4)	20,3	$C_{16}H_{17}N_5O_4$	20,4	53
VIIIj	174—175	45	3429	1702	258 (22,7)	14,8	$C_{22}H_{22}N_4O_2$	14,9	49

their isomers (Table 2). The corresponding azomethines VIf and g are precipitated in reasonably pure form on addition of a catalyst to alcoholic solutions of p- and m-dinitrobenzylideneacetones and the diamine I. This is probably because of the lower solubility of VIf and g; however, on subsequent warming to 40-50°, they dissolved and were converted to compounds VIIIf and g.

The absorption spectrum of compound VIII (Table 2) contains a very broad angle in the long-wave region with λ_{max} 258-274 nm, probably due to overlapping fields created by electronic transitions; there is no marked dependence on the nature of the substituent in the aromatic ring, as occurs in the azomethines VI. It follows from this that the conversion of compound VI to VIII involves the saturation of the benzylidene group C=C bond and a decrease in the length of the conjugated bond system. Characteristic of the infrared spectrum of compound VIII is the presence in the high-frequency region of absorption bands typical of associated hydroxyl groups, while no band could unambiguously be attributed to the νN—H group. A strong narrow band was present at ∿1700 cm^{-1}, the region in which carbonyl group absorption occurs. With the azomethines II-VI, or the dihydropyrimidinooxazepines VII [1], absorption in this region is generally more complex, apparently due to the interaction of the two carbonyl groups in the pyrimidine ring. From this it is concluded that compound VIII is 2-aryl-4,7,9-trimethyl-6-hydroxy-8-oxo-2,3-dihydropyrimidino[5,6-b]-1,5-diazepine, which exists mainly in the 6-hydroxy tautomeric form, due to the formation of intramolecular bonds as shown in the reaction scheme.

It is interesting to note that according to [3, 4], a number of syntheses based on the diamine I have been conducted in acid medium without hydrolysis of the 5-amino group occurring. For example, the reaction of I with acetyl acetone in refluxing acetic acid (7.5 h) gave lumazine [3]. It is also known [5] that the reaction of acetone or mesitylene oxide with the diamine I gives exclusively dihydropyrimidinodiazepine; this reaction is easily duplicated and compound VIII can be synthesized by a similar reaction. Thus, a sharp increase in the rate of hydrolysis of the 6-amino group is observed only in the reaction of the diamine I with chalcones. It is suggested that in the intermediate azomethines II, both aromatic rings promote the enolization of the 4-hydroxy group at the expense of intramolecular hydrogen bonding, and consequently increase the amount of 6-imino form capable of hydrolysis.

Earlier [6], while studying the base-catalyzed reaction of o-phenylidenamine with chalcones, the formation of intermediate β-amino adducts was noted. In the reaction of this diamine with acetylarenes in acid medium, the first step is a condensation reaction [7]; the experimental data above confirm that a similar process occurs in the reaction of the diamine I with carbonyl compounds.

EXPERIMENTAL

Infrared spectra were measured on a Specord IR-75 spectrophotometer (in KBr pellets); absorption spectra, on a Specord UV-Vis (in methanolic solutions with concentrations of $2\text{-}3\cdot10^{-5}$ mole/liter); mass spectra of compounds Vd and IX, on a Varian MAT CH-6 with direct introduction of the sample into the ion source (temperature of ionization chamber, 180°, ionizing potential 70 eV, emission current 100 mA, temperature to which samples were heated from 50-70°).

Compounds III and IV were synthesized by the method given in [1]; some properties of compound VII are also reported in this article.

6-Amino-5-(1-phenylcinnamylidenamino)-1,3-dimethyluracil (IIa). To a boiling solution of 0.5 g (3 mmoles) of the diamine I and 0.62 g (3 mmoles) of chalcone in 25 ml of methanol were added 1-2 drops of 0.1-0.2% alcoholic HCl solution, and after refluxing for 10-15 min, the solution was diluted with water and cooled. A mixture of yellow and white crystals of compounds IIa and VIIa were obtained; the large crystals of IIa were separated mechanically.

Mixtures of compounds IIc-e and VIIc-e were obtained in the same way.

6-Amino-5-(1-methyl-p-chlorobenzylidenamino)-1,3-dimethylyracil (Vd). Dry HCl was passed through a solution of 0.5 g (2.9 mmoles) of the diamine I in 20 ml of benzene; the precipitated salt was filtered off and dissolved in 30 ml of methanol containing 0.45 g (2.9 mmoles) of p-chloroacetophenone. The solution was refluxed for 1 h, cooled, and neutralized with ammonia to give 0.62 g (70%) of compound Vd, mass spectrum, m/z (%): 308 (17), 306 (50), 293 (33), 291 (100).

Compounds Vb, e-i, VIIa, and c-e were obtained in the same way.

Reaction of 6-amino-5-(1,4-dimethylbenzylidenamino)-1,3-dimethyluracil (Vb). A. A solution of 0.57 g (2 mmoles) of compound Vb, 0.21 g (2 mmoles) of benzaldehyde, and 0.2 ml of glacial acetic acid in 30 ml of methanol was refluxed for 1 h, cooled, and neutralized with ammonia. Light-yellow crystals of compound IIIa (0.41 g; 80%) were obtained. The filtrate was treated with an excess of a methanolic solution of 2,4-dinitrophenylhydrazine hydrochloride to give 0.6 g of the dinitrophenylhydrazone of p-methylacetophenone with mp 256-258° (literature value 257-258° [8]).

B. Using the same conditions, compound Vb and p-nitroacetophenone gave the azomethine Vf and p-methylacetophenone in quantitative yield.

6-Amino-5-(1-methylcinnamylidenamino)-1,3-dimethyluracil (VIa). A solution of 1.7 g (10 mmoles) of the diamine I and 1.46 g (10 mmoles) of benzylidenacetone in 40 ml of methanol was cooled to 5-10°, and 0.1 ml of glacial acetic acid was added. After 5-10 min, 60 ml of water was added to the solution, and the yellow crystals of VIa (1.8 g; 60%) were filtered off.

Compounds VIb, c, and j were obtained in the same way.

6-Amino-5-(1-methyl-p-nitrocinnamylidene)-1,3-dimethyluracil (If). To a solution of 1.91 g (10 mmoles) of p-nitrobenzylidenacetone and 1.7 g (10 mmoles) of the diamine I in 50 ml of methanol was added 0.1 ml of glacial acetic acid. The solution immediately turned claret-colored and the azomethine VIf precipitated out; yield 3.05 g (89%).

Compound VIg was obtained in the same way.

2-Phenyl-4,7,9-trimethyl-6-hydroxy-8-oxo-2,3-dihydropyrimidino[5,6-b]-1,5-diazepine (VIIIa). A solution of 1.46 g (10 mmoles) of benzylidenacetone and 1.7 g (10 mmoles) of the diamine I in 40 ml of methanol containing 0.2 ml of glacial acetic acid was allowed to stand at room temperature for 10-15 min, and the volume of the solution was reduced to 1/4 by blowing a stream of cold air through it. The light-yellow crystals which formed were filtered off and recrystallized from hexane to give 1.5 g (52%) of compound VIIIa.

Compounds VIIId and j were prepared in the same way.

2-(4-Nitrophenyl)-4,7,9-trimethyl-6-hydroxy-8-oxo-2,3-dihydropyrimidino[5,6-b]-1,5-diazepine (VIIIf). The reaction mixture, obtained during the synthesis of compound VIf, was heated for 30 min at 40-50° without filtering off the precipitate. Compound VIf gradually dissolved and the solution became clear. On cooling, yellow-brown crystals of compound VIIIf separated; yield 2 g (57%).

Compound VIIIg was prepared in the same way.

8-Phenyltheophylline (IX). A mixture of 0.5 g of the diamine I and 3 ml of acetophenone was refluxed for 2 h, cooled, and diluted with 10 ml of methanol. The precipitated material was filtered off to give 0.55 g (74%) of compound IX with mp > 300° (literature value, mp > 300° [9]), m/z 256 (100%).

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^{13}C NMR SPECTRA OF CYCLIC NITRONES.

1. 2-SUBSTITUTED 4-METHYL- AND 4-PHENYL-1-HYDROXY-5,5-DIMETHYL-3-IMIDAZOLINE 3-OXIDES

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UDC 543.422.25 + 547.781.3

The introduction of an N-oxide oxygen atom into azomethines leads to an upfield shift of the signals for the carbon atom of the C=N group in the ^{13}C NMR spectra by 30-33 ppm. This is consistent with the increase in the electron density on this atom. The signal of the nitrone carbon atom is observed in the region of 140-147 ppm, depending on the nature of the substituent at the C(2) atom of the 3-imidazoline 3-oxide ring.

Cyclic nitrones, which are heterocyclic compounds containing an azomethine N-oxide group, have a wide range of synthetic potentialities [1]. This is due to the fact that, as in the case of heterocyclic N-oxides [2], the N-oxide oxygen atom activates them with respect both to electrophilic and to nucleophilic and radical reagents. In addition, the ability of the nitrones to undergo 1,3- and 1,4-cycloaddition reactions makes it possible to use them in the synthesis of various heterocyclic systems, including natural compounds [3, 4]. There are no published data on the systematic investigation of compounds containing a nitrone group by ^{13}C NMR spectroscopy, whereas this method makes it possible not only to obtain valuable structural information but also to assess the electron density distribution in the ground state of the molecule [5, 6].

In the present work we begin a series of investigations into cyclic nitrones by ^{13}C NMR spectroscopy on the basis of 3-imidazoline 3-oxides in order to determine the characteristic range of chemical shifts (CS) of the carbon atoms of the nitrone group and also to study the effect of various factors (substituents, solvents, etc.) on the electron density distribution in the ground state of a molecule containing the nitrone group. In the present work we considered the effect of substituents at the second position of 3-imidazoline 3-oxide.

It is known that the N-oxide group in pyridine N-oxides has a strong electron-donating effect on the α- and γ-carbon atoms [7]. An effect similar in direction but larger in magnitude by virtue of its greater localization is observed in nitrones. Thus, during comparison of the spectra of the 3-imidazolines (Ia) and (IIIa) with the spectra of the corresponding 3-imidazoline 3-oxides (IIa) and (IVa) a strong screening effect on the C(4)

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