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REACTION OF 5,6-DIAMINO-1,3-DIMETHYLURACIL WITH ARYLIDENEACETONES AND ARYLIDENECYCLANONES

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The reaction of 5,6-diamino-1,3-dimethyluracil dihydrochloride with mono- and diarylideneacetones and with cyclohexanones give 2,4-disubstituted 1,7,9-triazaspiro[4,5]dec-1-ene-6,8,10-triones. It was found that arylidenecyclopentanones form only 5-azomethines with retention of the amino group at position 6 of the uracil ring.

In a previous report [1] we have shown by X-ray analysis that the reaction of 5,6-diamino-1,3-dimethyluracil (I) with chalcones leads to 2,4-diaryl-7,9-dimethyl-1,7,9-triazaspiro[4,5]dec-1-ene-6,8,10-triones and not to 2,3-dihydropyrimidino[5,6-b]-1,5-oxazepine derivatives [2]. The available spectral data corresponded with both indicated systems to an equal degree and, since we were unable to find literature analogs of the formation of a spiro compound in the reaction of *ortho*-diamines with unsaturated ketones, in [2, 3] we reported uncertain assignments of the product structures. At the same time the hydrolysis of the amino group in position 6 of uracil I had been confirmed for the conditions of the given reaction, even though a number of examples were known in which this group contributed to the synthesis of purine and lumazine derivatives [4, 5], pyrimidinodiazepines (*via* reaction with mesityl oxide and 2,3-dibromochalcones [6-8]), and azomethines [3]. The behavior of compound I was so varied and unexpected that we have been obliged to carry out an investigation of its reactive properties.

The aim of the present work was a study of the structure of the compounds obtained by reaction of the dihydrochloride of diamine I (II) with mono- and diarylideneacetones (IIIa-d) and with cyclanones (IV, Va,b). Experiments relating to the same reaction of diamine I (base) have shown that the reactivity is lower than that of the dihydrochloride II (processes being several times slower) and this also served as a reason for choosing the salt II as reagent.

We have shown that the reaction of salt II with ketones IIIa-d by refluxing in methanol in the presence of a small amount of acetic acid gives the spiro compounds VIa-d, which were identified by their IR and PMR spectral data and through the results of elemental analysis for nitrogen (Table 1). The process demands more prolonged refluxing of the reaction mixture (about 3 h) when compared with the analogous reaction for chalcones. In addition, the yields of the spiro compounds VIa-d are significantly lower and this may be explained by the lower thermodynamic stability of the intermediate azomethines.

The IR spectra of the products VIa-d show strong carbonyl group stretching absorptions at 1640-1750 and the C=N group at 1600-1650 as well as the absence of primary or secondary amino group absorption at 3100-3600 cm^{-1}.

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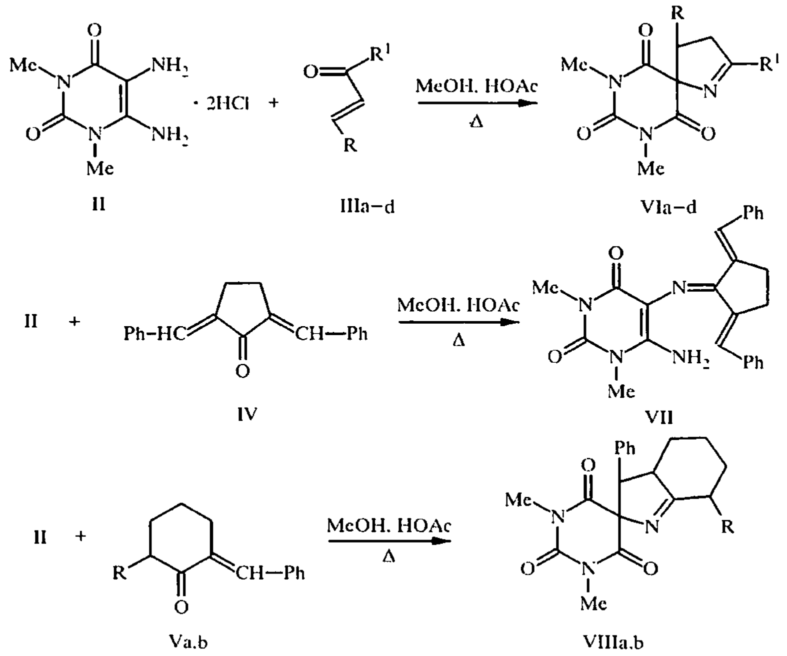

III, VI a,c R = Ph, b,d R = 4-MeOC$_6$H$_4$; a,b R^1 = Me, c R^1 = PhCH=CH, d R^1 = 4-MeOC$_6$H$_4$CH=CH;
V, VIIIa R = H, b R = C$_6$H$_4$CH=

The PMR spectra of compounds VIa-d in the deuteromethanol solutions show signals typical of an ABX type system, i.e. a double doublet for the protons of the methylene group at 2.99-3.91 and a double doublet for the methine proton at 3.83-3.97 ppm (Table 2). The vinyl protons of the R^1 substituent in compounds VIc,d are *trans* orientated as evidenced by the spin-spin couplings (^3J) of 16.1 and 18.2 Hz respectively.

Hence the spectral data confirm the formation in the reaction of salt II with the unsaturated ketones III of 2,4-disubstituted 1,7,9-triazaspiro[4,5]dec-1-ene-6,8,10-triones (VIa-d).

TABLE 1. Parameters for Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, % N	mp, °C	IR spectrum, cm^{-1} $\nu_{C=O}$	IR spectrum, cm^{-1} $\nu_{C=N}$	UV spectrum, λ_{max}, nm, ($\varepsilon \times 10^{-3}$) in ethanol	Yield, %
I	$C_{16}H_{17}N_3O_4$	43.61 43.81	189-190	1748 1682	1642	—	25
II	$C_{17}H_{19}N_3O_4$	54.68 55.49	191-193	1736 1670	1645	—	17
III	$C_{23}H_{21}N_3O_5$	47.90 47.99	220-222	1748 1683	1638	228 (9.9) 289 (13.3)	51
IV	$C_{25}H_{25}N_5O_5$	48.23 49.24	222-224	1744 1683	1638	317 (23.6)	53
V	$C_{25}H_{24}N_4O_2$	52.68 52.68	>310	1715 1683	1603	—	20
IV	$C_{19}H_{21}N_3O_3$	48.23 49.24	175-177	1648 1715	1603	257 (24.7)	68
V	$C_{26}H_{25}N_3O_3$	52.68 52.68	302-304	1695 1748	1622	233 (11.8)	65

TABLE 2. Chemical Shift δ (ppm) and Spin-Spin Coupling (*J*, Hz) for Compounds VIa-d

Compound	CH_3 (R^1), s	$2NCH_3$ two s	OCH_3 (in R), s	CH=CH		H_X, dd
				α, d	β, d	
VIa	2.26	2.59; 3.23	—	—	—	3.90
VIb	2.25	2.65; 3.22	3.70	—	—	3.83
VIc	—	2.63; 3.21	—	7.25	7.38	3.97
VId	—	2.68; 3.25	3.71*	7.30	7.38	3.89

Compound	H_A, dd	H_B, dd	H_{Ar}, m	J_{AB}	J_{AX}	J_{BX}	$J_{\alpha\beta}$
VIa	3.22	3.04	7.24-7.09	-17.3	8.8	10.2	—
VIb	3.12	2.99	6.76-6.98	-17.4	8.8	10.1	—
VIc	3.50	3.43	7.09-7.63	-16.0	8.0	10.0	16.1
VId	3.91	3.86	6.80-7.57	-13.6	8.75	10.5	18.2

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* Singlet signal for the OCH_3 group in R^1 is observed at 3.78 ppm.

The reaction of salt II under analogous conditions with cyclic unsaturated ketones IV and Va,b (which have a fixed s-*cis* enone structure) gives products whose structure depends on the starting ketone. In the case of the dibenzylidenecyclopentanone IV only the azomethine VII was obtained. Attempts to cyclize it proved unsuccessful. Formation of azomethines has also been observed by the authors of a report [4] on the reaction of diamine I with chalcones. In addition, we have repeated these results in the case of both chalcones and arylideneacetones. In all these cases an amino group unambiguously appears in the spectroscopic parameters (IR and PMR spectra) of the products formed. All of this points to the general nature of the reaction of unsaturated ketones with diamine I as occurring *via* a stage of an azomethine formation at the 5-amino group both for aromatic [1] and for cyclic α,β-unsaturated ketones.

At the same time, by reaction of salt II with mono- and dibenzylidenecylohexanones Va,b, there are formed the colorless spiro compounds VIIIa,b. Their IR spectra show characteristic CO group absorption bands at 1715-1742, CN absorption at 1604 (VIIIa) or 1622 (VIIIb), and the absence of absorption in the region 3200-3500 cm^{-1}. The PMR spectrum of compound VIIIa contains signals for the protons of all the fragments proposed for its structure, i.e. two methyl group singlets (3.23 and 3.41 ppm), an eight proton multiplet for the cyclohexane ring protons ($4CH_2$, 1.43-2.75 ppm), a singlet signal for the C$\underline{H}$Ph group in the five membered heterocycle (6.38 ppm), a quartet for the other methine proton in the same heterocycle (6.27 ppm), and a multiplet for the protons of the phenyl substituent (7.16-7.38 ppm). The mass spectral data for compound VIIIb does not disagree with this structure. The spectrum shows peaks with m/z 428.3 (100%) $[M+H]^+$, 426.5 (89%) $[M-H]^+$, 425.5 (58%) $[M-2H]^+$, 423.8 (64%) $[M-4H]^+$.

The given experimental facts can be understood if one bears in mind that the formation of azomethines and spiro compounds based on them involve a marked equilibrium character. This is indicated, for example, by the recyclization of the spiro system noted in study [1] which occurs upon prolonged refluxing of the reaction mixture. This is probably due to the fact that formation of the spiro system destroys the thermodynamically stable conjugated systems of the unsaturated ketone and derived azomethine. Together with the possible recyclization of the spiro compound [1] this explains the low yields of the spiro compounds described here, in particular VIa,b (25 and 17% respectively).

Such reactions are also sensitive to stereochemical factors and, because annelation of the pyrrole ring with cyclopentane having two sp^2 centers causes a significant increase of angular strain in the spiro compound, the process is halted at the stage of the azomethine VII formation. Increase in the size of the carbocycle relieves this problem and formation of the spiro products VIIIa,b occurs in good yields (68 and 65% respectively).

EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 instrument in KBr tablets. Electronic absorption spectra were obtained on a Specord M-40 instrument for solutions in ethanol at a substance concentration of 1-5 × 10^{-5} M. PMR spectra were taken on Bruker WP-200 and Varian VXR-300 instruments using DMSO-d_6, methanol-d_4, and pyridine-d_5 solvents with TMS internal standard. Mass spectra were measured on an MSBK mass spectrometer produced by "Electron" company (Sumy, Ukraine). Ionization of the substances was carried out by bombardment with ^{252}Cf fission fragments. The particle ionization energy was 90-110 MeV. The length of the tube was 45 cm and the accelerating intensity 20 kV. The accumulating time for the spectra was 15-20 min.

Monitoring of the purity of the compounds obtained was performed using TLC on Silufol UV-254 plates using chloroform, acetone, ethyl acetate, and methanol as solvents.

2,7,9-Trimethyl-4-phenylspiro[4,5]dec-1-en-6,8,10-trione (VIa). A solution of salt II (0.3 g, 1.2 mmol), benzalacetone (IIIa, 0.2 g, 1.2 mmol), and glacial acetic acid (0.4 ml) in methanol (20 ml) was refluxed for 3 h. After cooling, the reaction mixture was filtered to give colorless crystals of product VIa.

Compounds VIb-d and VIIIa,b were synthesized from salt II and the corresponding ketones IIIb-d and Va,b.

6-Amino-5-(2,5-dibenzylidenecyclopentylideneamino)-1,3-dimethyluracil (VII). A solution of salt II (0.3 g, 1.2 mmol), dibenzylidenecyclopentanone (IV, 0.31 g, 1.2 mmol), and glacial acetic acid (0.4 ml) in methanol (20 ml) was refluxed for 20 h. The precipitated crystalline product VII was filtered off and recrystallized from methanol.

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