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Conversion of 2-Aryl-4-dichloromethylen-5(4*H*)oxazolones to 5-Acylamino-Substituted Pyrimidine Bases

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Abstract—Available polycentral unsaturated azlactones with 4-dichloromethylene group by successive treating with benzamidine and then with morpholine or its analogs were converted to substituted 5-acylamino-4-hydroxypyrimidines containing the residues of the corresponding nitrogen bases in the position 6. The structure of these cyclization products is consistent with the scheme of their preparation and has been confirmed also by ^{1}H NMR spectroscopy and XRD analysis.

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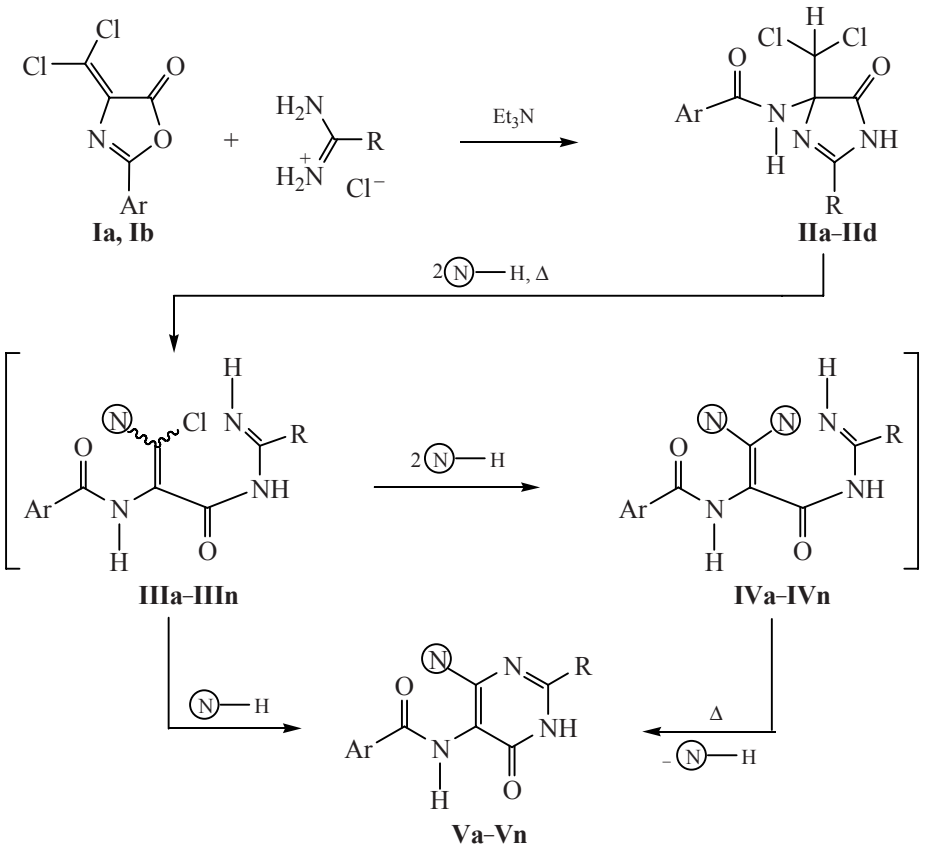
Chlorine-containing unsaturated azlactones **I** presented in the scheme are formed easily from the available chloralamides as described previously [1, 2]. Polycentral electrophilic reagents **I** have already found application for preparation of derivatives of 1,3-oxazole [1,3], 1,3-thiazole [4], 1,3,4-oxadiazole [5], 1,3,4-thiadiazole [6], oxazolo[4,5-*d*]pyrimidine [7], and some other fused systems [8].

In this study they were used in the development of a peculiar method for preparation of new three- and tetrafunctionalyzed pyrimidine derivaties as seen from the structures **I–V** (see the scheme and Table 1). At first the reagents **I** were converted by means of the reported procedure [9] to 4,5-dihydro-1*H*-imidazol-5 (4)-one derivatives **II** which were heated with morpholine, piperidine, or pyrrolidine to form the corresponding 5-acylamino-substituted pyrimidine bases **V** in the 40–67% yield.

In the complex transformation **II→V** three main processes take place. At first one or two chlorine atoms of dichloromethyl group in the compounds **II** are substituted by the residues of nitrogen-containing bases. The second step is the cleavage of the imidazoline ring, while the third one is the cyclization to substituted pyrimidines. Sequence of these stages is not established reliably, but enamides **III** or **IV** are probably the important precursors of recyclization. Structure of the final cyclization products agrees with ^{1}H NMR data (Table 2), and also with the results of X-ray study of one of the compounds **V** where Ar = 4-MeC_6H_4, R = H_2N, Ⓝ = $O(CH_2)_4N$. A general view of this molecule, and also the main interatomic distances and bond angles are presented in the figure.

The central heterocycle $N^2N(3)C(9\text{-}12)$ is planar. Deflections of atoms from the root-mean-square plane do not exceed 0.046 Å. Benzene ring C^{1-6} is practically orthogonal to this cycle, the corresponding dihedral angle is 81.0°. N^1, N^2, and N^5 nitrogen atoms within the limits of experimental error have the flat trigonal bond configuration while the bond configuration of N^4 atom is the flattened pyramide. Sums of the corresponding bond angles at these atoms are 358.9, 359.1, 357.3, and 349.8°, respectively. Conjugation of the UEP of N^1 atom with π-system of the $C^8{=}O^1$ double bond causes significant shortening of the $N^1{-}C^8$ bond [1.360(6) Å] as compared to the standard value for the $N(sp^2){-}C(sp^2)$ bond (1.43-1.45 Å) [10]. Molecular conformation is quite favorable for such interaction because $O^1{-}C^8{-}N^1{-}C^9$ torsion angle is only ~1.33°. Shortening of $N^4{-}C^{11}$ bond to 1.351(5) Å is explained analogously.



I: Ar = Ph (**a**), 4-MeC_6H_4 (**b**). II: Ar = Ph (**a, c**), 4-MeC_6H_4 (**b, d**); R = Ph (**a, b**), H_2N (**c, d**). **III–V**: Ar = Ph (**a, c, e, h, j, l, m**), 4-MeC_6H_4 (**b, d, f, g, i, k, m**); R = Ph (**a, b, e, f, h, i, l–n**); H_2N (**c, d, g, j, k**); (N) = $(CH_2)_4N$ (**a–d**), $(CH_2)_5N$ (**e–g**), $O(CH_2)_4$ (**h–k**), $PhCH_2NH$ (**l, m**), $PhCH_2CH_2NH$ (**n**).

Table 1. Yields, constants, and elemental analysis data of the compounds synthesized **Va–Vn**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
Va	55	>300 (DMF)	69.70	5.41	15.32	$C_{21}H_{20}N_4O_2$	69.98	5.59	15.54
Vb	44	>300 (dioxane)	70.25	5.76	14.73	$C_{22}H_{22}N_4O_2$	70.57	5.92	14.96
Vc	42	>300 (DMF)	59.82	5.55	23.26	$C_{15}H_{17}N_5O_2$	60.19	5.72	23.40
Vd	67	276-278 (EtOH)	61.01	5.92	22.19	$C_{16}H_{19}N_5O_2$	61.33	6.11	22.35
Ve	61	284–286 (EtOH)	70.69	6.09	14.88	$C_{22}H_{22}N_4O_2$	70.57	5.92	14.96
Vf	65	300–302 (EtOH)	69.98	6.07	14.33	$C_{23}H_{24}N_4O_2$	71.11	6.23	14.42
Vg	62	>300 (EtOH)	62.02	6.25	21.08	$C_{17}H_{21}N_5O_2$	62.37	6.47	21.39
Vh	47	>300 (AcOH)	66.89	5.24	14.70	$C_{21}H_{20}N_4O_3$	67.01	5.36	14.88
Vi	47	>300 (AcOH)	67.49	5.52	14.28	$C_{22}H_{22}N_4O_3$	67.67	5.68	14.35
Vj	40	>300 (DMF)	56.89	5.21	22.15	$C_{15}H_{17}N_5O_3$	57.14	5.43	22.21
Vk	56	288–289 (EtOH)	58.18	5.67	21.11	$C_{16}H_{19}N_5O_3$	58.35	5.81	21.26
Vl	11	>300 (DMF)	72.50	4.90	14.02	$C_{24}H_{20}N_4O_2$	72.71	5.08	14.13
Vm	21	>300 (DMF)	72.92	5.23	12.43	$C_{25}H_{22}N_4O_2$	73.15	5.40	13.65
Vn	15	>300 (DMF)	72.01	5.19	13.38	$C_{25}H_{22}N_4O_2$	73.15	5.40	13.65

Table 2. Spectral data of the compounds synthesized

Comp. no.	^{1}H NMR spectrum, δ, ppm (DMSO-d_6)
Va	1.84 br.s, 3.64 br.s [8H, $(CH_2)_4N$], 7.50–8.20 m (10H, $2C_6H_5$), 9.33 s (1H, NH), 12.20 br.s (1H, NH)
Vb	1.81 br.s, 3.61 br.s [8H, $(CH_2)_4N$], 2.38 s (3H, CH_3), 7.30–8.16 m (9H, C_6H_5, C_6H_4), 9.22 s (1H, NH), 12.20 br.s (1H, NH)
Vd	1.71 br.s, 3.60 br.s [8H, $(CH_2)_4N$], 2.36 s (3H, CH_3), 6.16 c (2H, NH_2), 7.26–7.83 m (4H, C_6H_4), 8.83 s (1H, NH), 10.10 br.s (1H, NH)
Ve[a]	1.55 m, 3.65 br.s [10H, $(CH_2)_5N$], 7.44–8.15 m (10H, $2C_6H_5$), 9.24 c (1H, NH), 12.27 br.s (1H, NH)
Vf[a]	1.53 br.s, 3.64 br.s [10H, $(CH_2)_5N$], 2.39 s (3H, CH_3), 7.25–8.15 m (9H, C_6H_5, C_6H_4), 9.15 s (1H, NH), 12.26 br.s (1H, NH)
Vh[a]	3.61 m [8H, $O(CH_2)_4N$], 7.55–8.13 m (10H, $2C_6H_5$), 9.36 s (1H, NH), 12.37 br.s (1H, NH)
Vi	2.40 s (3H, CH_3), 3.61–3.67 m [8H, $O(CH_2)_4N$], 7.26–8.15 m (9H, C_6H_5, C_6H_4), 9.15 s (1H, NH), 12.29 br.s (1H, NH)
Vk	2.38 s (3H, CH_3), 3.49 m [8H, $O(CH_2)_4N$], 6.17 br.s (2H, NH_2), 7.24–7.82 m (4H, C_6H_4), 8.79 s (1H, NH), 10.27 br.s (1H, NH)
Vl	4.67 s (2H, CH_2), 7.20–8.10 m (16H, $3C_6H_5$, NH), 9.18 c (1H, NH), 12.15 br.s (1H, NH)
Vm	2.30 s (3H, CH_3), 4.69 s (2H, CH_2), 6.90 br.s (1H, NH), 7.20–8.10 m (14H, $2C_6H_5$, C_6H_4), 8.8 br.s (1H, NH), 11.25 br.s (1H, NH)
Vn	2.88 br.s (2H, CH_2), 3.65 br.s (2H, CH_2), 6.67 br.s (1H, NH), 7.20–8.10 m (15H, $3C_6H_5$), 9.01 c (1H, NH), 12.05 br.s (1H, NH)

[a] IR spectra of compounds **Ve, Vf,** and **Vh**, ν, cm^{-1}: 1630 (NC=O), 3050–3400 (NH_{ac}).

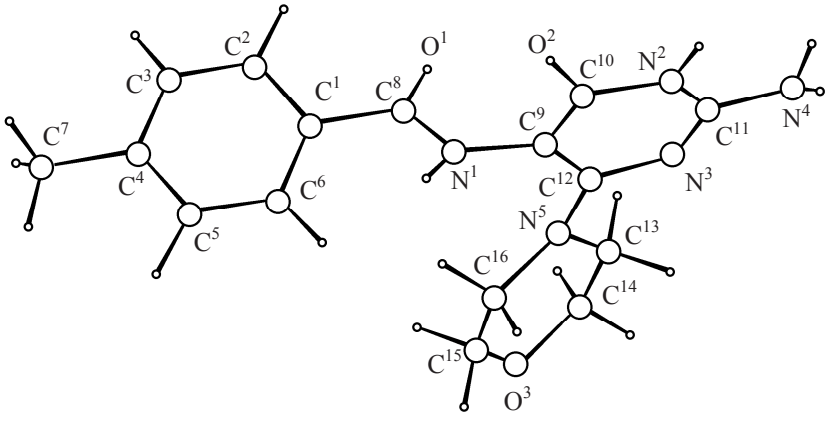
Hence, the presented data confirm not only the structure of compound **Vk**, but also of its close and more remote analogs.

Finally note that the sphere of application of the chlorine-containing azlactones for preparation of 5-acylamino-substituted pyrimidine bases is evidently wider than it is established in this work, but the attempts to involve some simplest primary and secondary amines failed. Treating compounds **II** with benzylamine and 2-phenylethylamine lead to low yield of the final products **V**. Meanwhile even with the above-mentioned limitations the transformation **I**→**V** is an important extension of the existing methods of the acylamino groups introduction in the position 5 of pyrimidine bases (compare [11]).

EXPERIMENTAL

IR spectra were obtained on a Specord M-80 spectrometer in KBr pellets. ^{1}H NMR spectra were taken on a Varian VXR-300 instrument in DMSO-d_6 against internal TMS.

X-ray study of the single crystal of compound **Vk** (0.07×0.31×0.49 mm) was carried out at room temperature on an automatic CCD Bruker Apex II



General view of the molecule of compound **Vk**. Interatomic distances (Å) and bond angles (deg): O^1–C^8 1.212(5), C^1–C^8 1.486(6), N^1–C^8 1.360(6), N^1–C^9 1.430(5), N^2–C(10) 1.386(5), N^2–C^{11} 1.340(5), N^3–C^{11} 1.307(5), N^3–C^{12} 1.367(5), N^4–C^{11} 1.351(5); $C^8N^1C^9$ 121.2[4], $C^{10}N^2C^{11}$ 121.9[4], $C^{11}N^3$C-12 117.4(4).

diffractometer (MoK_α-radiation, λ 0.71069 Å, θ_{max} 24.4°, $-20 \le h \le 18$, $-14 \le k \le 12$, $-16 \le l \le 16$). 13950 reflections were collected (2617 independent, R_{int} 0.02). Crystals of compound **Vk** are rhombic, *a* 17.7261(7), *b* 12.3434(5), *c* 14.5632(6) Å, *V* 3186.4(2) Å^3, *M* 329.4, Z 8, d_{calc} 1.37 g cm^{-3}, μ 0.98 cm^{-1}, *F*(000) 1392, space group *Pbcn* (N 60). The structure was solved by the direct method and refined by the root-mean-square method in the full-matrix anizotropic approximation using CRYSTALS complex of programs [12]. In the refining procedure 1241 reflections with $I > 2\sigma(I)$ were used (233 refined parameters, number of reflections per one parameter 5.3). About 50% of hydrogen atoms were evaluated from the differential synthesis of electronic density, the other atoms were settled geometrically. All hydrogen atoms were included in refining with fixed positional and thermal parameters, only H^1, H^2, H^{41}, and H^{42} atoms were refined isotropically. During the refining the Chebyshev weighting scheme [13] with five parameters (1.20, 1.10, 1.11, 0.35, and 0.29) was used. Final values of divergence factors are *R* 0.056, R_W 0.059, *GOF* 1.167. Residual electronic density from the differential Fourier synthesis is 0.23 and –0.20 e Å^{-3}. Complete set of X-ray data for the compound **Vk** was deposited in the Cambridge bank of structural data (CCDC 694987).

5-Acylamino-6-pyrrolidino(piperidino, morpholino)-2-phenylpyrimidin-4(3*H*)-ones (Va, Vb, Ve, Vf, Vh, Vi). A mixture of 0.03 mol of one of the compounds **IIa** and **IIb** [9] and 0.6 mol of pyrrolidine, piperidine, or morpholine was refluxed for 12 h. After cooling the amine excess was removed in a vacuum, the residue was treated with water, and the precipitate formed was filtered off. Compounds **Va, Vb, Ve, Vh,** and **Vi** were purified by crystallization.

2-Amino-5-acylamino-6-pyrrolidino(piperidino, morpholino)pyrimidin-4(3*H*)-ones (Vc, Vd, Vg, Vj, Vk) were prepared analogously to **Va, Vb, Ve, Vh,** and **Vi** from compounds **IIc** and **IId**.

5-Acylamino-6-benzylamino(phenylethylamino)-2-phenylpyrimidin-4(3*H*)-ones (Vl-Vn). A mixture of 0.03 mol of one of compounds **IIa** and **IIb** and 0.3 mol of benzylamine or phenylethylamine in 20 ml of dry dioxane was refluxed for 16 h. After cooling solvent was removed in a vacuum, the residue was treated with water, the precipitate was filtered off, and compounds **Vl-Vn** were purified by crystallization.

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