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# ACYLATION OF PHENACYLPYRIMIDINES

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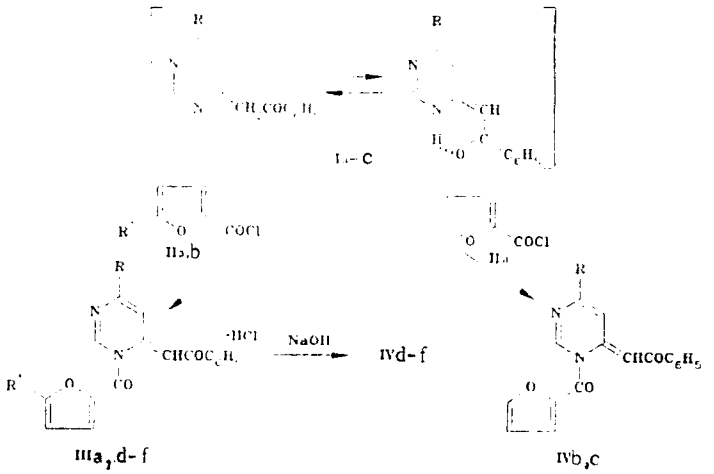
UDC 547.853.4'724.07

The reaction of phenacylpyrimidines with 2-furancarboxylic chlorides was studied. 1-Furoylphenacylidenepyrimidines were obtained.

For further study of the chemical properties of the pyrimidine-series ketones that we prepared previously [1, 2], we investigated the acylation of phenacylpyrimidines by 2-furancarboxylic chlorides.

In the reaction of phenacylpyrimidines Ia-c with acid chlorides IIa and IIb, we obtained the corresponding 1-furoylphenacylidenepyrimidines IVa-f:




I a $R=N(CH_3)_2$, b $R=OCH_3$, c $R=CH_2COC_6H_5$; II a $R^1=H$, b $R^1=NO_2$; III a, IV a $R=N(CH_3)_2$, $R^1=H$; IV b $R=OCH_3$, $R^1=H$; IV c $R=CH_2COC_6H_5$, $R^1=H$; III d, IV d $R=N(CH_3)_2$, $R^1=NO_2$; III e, IV e $R=OCH_3$, $R^1=NO_2$; III f, IV f $R=CH_2COC_6H_5$, $R^1=NO_2$

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TABLE 1. Parameters of Proton NMR Spectra of Compounds Ia and IVa ($CDCl_3$)

| Compound | Chemical shifts, δ, ppm | | | | | |
|---|---|---|---|---|---|---|
| | 2-H* (s) | 5-H (s) | $CH_3$ (s) | $-CH_2-$ (s) | $-N(CH_3)_2$ (s) | other signals |
| Ia | 8,48; 8,30 | 6,33; 5,93 | 4,20 | 5,80 | 3,05; 3,01 | 7,30 ... 8,0 (m, $C_6H_5$) |
| IVa | 8,40 | 6,64 | — | 6,70 | 2,91 | 7,30 ... 7,80 (m, $C_6H_5$, 3-, 5-H of furan); 6,55 (q, 4-H of furan) |

*Denotes insignificant (≤1 Hz) doubling or broadening of singlet signals of protons in the 2 and 5 positions of the pyrimidine ring (see text).

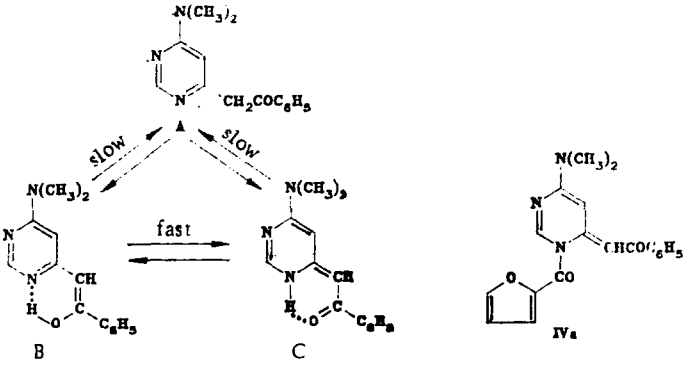
The reaction of phenacylpyrimidines with furancarboxylic chlorides occurs under different conditions in relation to the nature of the substituents in the pyrimidine and furan rings. Phenacylpyrimidines Ib and Ic react with chloride IIa only in the presence of a base. The reaction of compound Ia with chloride IIa occurs in the absence of a base. The latter fact can be explained by the presence of a strong electron-donor group in the 4 position of the pyrimidine ring facilitating the electrophilic attack of the acid chloride.

Compounds Ia-c react with acid chloride IIb without a base because the acid chloride containing a nitro group in the 5 position of the furan ring is more electrophilic than IIa.

1-Furoylphenacylidenepyrimidines IVa-f, obtained by the reaction of phenacylpyrimidines with furancarboxylic chlorides, are facilely hydrolyzed by water with the formation of starting phenacylpyrimidines Ia-c.

The structure of the obtained compounds was confirmed by the data of elemental analysis and by proton NMR and IR spectra. The IR spectra of compounds III and IV contained absorption bands at 1640 $cm^{-1}$ (C=O). The position of the furoyl group in compounds IVa-f was proven for the case of N-substituted derivative IVa by comparison of the proton NMR spectra of starting phenacylpyrimidine Ia and compound IVa (Table 1).

Previously [3-5] it was shown that trichloroacetonyl- and phenacylpyrimidines are in three tautomeric forms: ketone (A), enol (B), and ylidene (C). The data of the proton NMR spectra suggest that for compound Ia in $CDCl_3$ there is also equilibrium of the three tautomeric forms:




The proton NMR spectrum of compound Ia in $CDCl_3$ contained a singlet signal of methylene protons at 4.2 ppm (form A). Because of rapid exchange of the chelated proton (according to the IR spectra in $CCl_4$ the free NH group was not manifested up to concentration $10^{-4}$ M and temperature 70°C), the signal of the methine proton was averaged for the enol (B) and pyrimidinylidene (C) forms and was observed at 5.8 ppm. The proton NMR spectrum of compound Ia contained two signals each of the protons of the dimethylamino group and the protons in the 2 and 5 positions of the pyrimidine ring, corresponding to the tautomeric forms A and (B + C) (Table 1). The ratio of the integrated intensities of the signals of the ketone form (A) and the sum of the enol and ylidene (B + C) forms made it possible to determine the ratio of the tautomers A and (B + C), equal to 42:58 (±1%).

TABLE 2. Characteristics of Synthesized Compounds IIIa, IIId-f, and IVa-f

| Compound | mp, °C | Found, % | | | Empirical formula | Calculated, % | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | | C | H | N | |
| IIIa | 181...183 (decomp.) | 61.2 | 4.9 | 10.9 | $C_{19}H_{17}N_3O_3 \cdot HCl$ | 61.4 | 4.9 | 11.3 | 87 |
| IIId | 138...140 (decomp.) | 54.1 | 4.1 | 13.4 | $C_{19}H_{16}N_4O_5 \cdot HCl$*2 | 54.7 | 4.1 | 13.4 | 58 |
| IIIe | 184...187 (decomp.) | 53.2 | 3.2 | 10.4 | $C_{18}H_{13}N_3O_6 \cdot HCl$*3 | 53.5 | 3.5 | 10.4 | 64 |
| IIIf | 194...198 (decomp.) | 60.7 | 3.4 | 8.37 | $C_{25}H_{18}N_3O_6 \cdot HCl$*4 | 61.0 | 3.7 | 8.54 | 54 |
| IVa | 135...138*1 | 68.6 | 5.3 | 12.6 | $C_{19}H_{17}N_3O_3$ | 68.1 | 5.1 | 12.5 | 67 |
| IVb | 96...98*1 | 66.9 | 4.4 | 8.5 | $C_{19}H_{17}N_3O_3$ | 67.1 | 4.4 | 8.7 | 68 |
| IVc | 142...144*1 | 73.1 | 4.5 | 6.6 | $C_{25}H_{18}N_2O_4$ | 73.1 | 4.4 | 6.8 | 61 |
| IVd | 116...118*1 | 59.9 | 4.4 | 14.3 | $C_{19}H_{16}N_4O_5$ | 59.9 | 4.2 | 14.7 | 28 |
| IVe | 155...156*1 | 59.0 | 3.6 | 11.1 | $C_{18}H_{13}N_3O_6$ | 58.8 | 3.6 | 11.4 | 59 |
| IVf | 168...169*1 | 66.1 | 3.9 | 9.1 | $C_{25}H_{17}N_3O_6$ | 65.9 | 3.8 | 9.3 | 57 |

*1Crystallization conditions: compounds IVa-d from petroleum ether; IVe from a mixture of benzene and petroleum ether, 1:1; and IVf from acetonitrile.
*2Found: Cl 8.5%; calculated: Cl 8.5%.
*3Found: Cl 8.2%; calculated: Cl 8.8%.
*4Found: Cl 7.1%; calculated: Cl 7.2%.

In the proton NMR spectrum of N-furoylphenacylidenepyrimidine IVa the signal of the methine proton was observed at 6.7 ppm. The low-field shift of the signal of the methine proton in going from compound Ia to IVa was 0.9 ppm and confirmed the presence of an electron-acceptor furoyl group at $N_{(1)}$ of the pyrimidine ring in compound IVa. The proton NMR spectrum of this compound contained a singlet signal of the dimethylamino group (2.91 ppm). The complex multiplet in the region of phenyl protons included signals of protons in the 3 and 5 positions of the furan ring [6]. The signal of the proton at $C_{(4)}$ of the furan ring was observed at 6.55 ppm. Insignificant doubling of the signals of the protons at $C_{(2)}$ and $C_{(5)}$ of the pyrimidine ring (and also of the corresponding signals in compound Ia) was probably related to cis-trans isomerism of the side chain in the 6 position of the pyrimidine ring.

The obtained compounds manifested no activity with respect to lymphoid leukosis P-388 in a total dose of 2000 mg/kg.

## EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer in KBr tablets, the proton NMR spectra were recorded on a Bruker WP-200 spectrometer in $CDCl_3$, and the external standard was hexamethyldisiloxane (HMDS).

Phenacylpyrimidines Ia-c were prepared according to [1] and [2]. The characteristics of synthesized compounds IIIa, IIId-f, and IVa-f are given in Table 2.

General Procedure for Preparation of 1-(5'-$R^1$-2'-Furoyl)-4-R-6-phenacylidenepyrimidine Hydrochlorides IIIa and IIId-f. A solution of 2.5 mmoles of acid chlorides IIa and IIb in 10 ml of dry acetonitrile was added dropwise for 30 min to a solution of 2.5 mmoles of phenacylpyrimidine Ia, Ib, or Ic in 40 ml of dry acetonitrile. The mixture was kept at 20°C for 10 h. The precipitate was filtered off, washed with diethyl ether, and dried in air. The reaction products IIIa and IIId-f were purified by reprecipitation from methanol by diethyl ether.

1-(5'-$R^1$-2-Furoyl)-4-R-6-phenacylidenepyrimidines (IVa, IVd, and IVc). Hydrochlorides IIIa and IIId-f (1 mmole) were dissolved in 20 ml of chloroform and the whole was shaken with 10 ml of a 1 N NaOH solution. The water–alkali layer was separated and extracted with chloroform (3 × 10 ml), and the extract was dried with magnesium sulfate and evaporated. The residue was treated with 150 ml of hot petroleum ether. The precipitate was filtered off and crystallized from the appropriate solvents. Proton NMR spectrum of compound IVd: 3.5 (6H, singlet, $N(CH_3)_2$); 7.0 (1H, singlet, =CH); 7.2 (1H, singlet, 5-H) 7.7...8.03 (7H, multiplet, $C_6H_5$, 3-, 4-H of furan); 8.8 ppm (1H, singlet, 2-H).

1-(5'-$R^1$-2'-Furyol)-4-R-6-phenacylidenepyrimidines (IVb) and (IVc). To a solution of phenacylpyrimidine Ib or Ic and 2 moles of pyrimidine in 20 ml of dry benzene, 2 mmoles of

acid chloride IIb was added dropwise with stirring for 30 min. The reaction mixture was stirred for 5 h more at 20°C. Pyridine hydrochloride was filtered off, and the filtrate was evaporated in the vacuum of an aspirator. The residue was boiled with 150 ml of petroleum ether. After cooling of the extract, the precipitate was filtered off and crystallized from the appropriate solvent. Proton NMR spectrum of compound IVb: 3.87 (3H, singlet, $OCH_3$); 6.57 (1H, quadruplet, 4-H of furan); 6.75 (1H, singlet, =CH); 6.86 (1H, singlet, 5-H); 7.29...7.65 (7H, multiplet $C_6H_5$, 3-, 5-H of furan); 8.55 ppm (1H, singlet, 2-H).

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# REACTIONS OF ARYLHYDRAZINES WITH α-FORMYL DERIVATIVES OF SIX- AND SEVEN-MEMBERED RING LACTAMS


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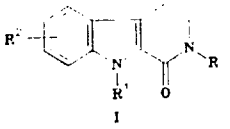
Reactions of α-formyl derivatives of N-methyl-δ-valerolactam and N-methyl-ε-caprolactam with arylhydrazines lead to the formation of 3,4,5,10-tetrahydroazepino[3,4-b]indole-1(2H)-one and 2,3,4,5,6,11-hexahydro-1H-azocino[3,4-b]indol-1-one derivatives. As the size of the lactam ring is increased the role of competing reactions, such as dealkylation at the indole nitrogen atom and the formation of 5-pyrazolone via reaction with α-unsubstituted phenylhydrazine, also increases.


In previous papers [1, 2] we have investigated the reactions of α-formyl-γ-lactam enamines with arylhydrazines, which lead to a series of 1-oxo-1,2,3,4-tetrahydro-β-carbolines I in high yields.



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It was of interest to us to expand the scope of these reactions to include formyllactam derivatives of greater ring size. Success in this area would provide an approach to the preparation of azepino[3,4-b]indole derivatives, which are interesting from the point of view of their biological activity, as well as to derivatives of a previously unknown heterocyle, namely, azocino[3,4-b]-indole.

In the present paper we have examined the reactions of arylhydrazines with α-hydroxymethylene-N-methyl-δ-valerolactam (II), α,α'-hydroxybis(1-methyl-3-methylene-2-piperidone) (III), and an enamine of α-formyl-N-methyl-ε-caprolactam (IV), prepared via Villsmaier formylation of the corresponding N-methyllactams [3].


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