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# IMINE–ENAMINE TAUTOMERISM OF DIHYDROAZOLOPYRIMIDINES. 6.* SYNTHESIS AND TAUTOMERISM OF THIENYL DERIVATIVES OF DIHYDRO-1,2,4-TRIAZOLO-[1,5-*a*]PYRIMIDINES

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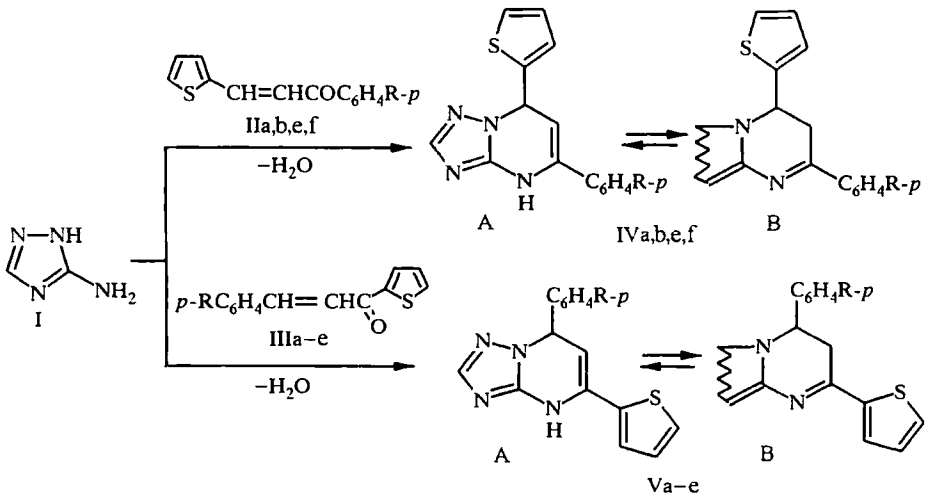
*The cyclocondensation of thiophene analogs of chalcone with 3-amino-1,2,4-triazole gives 5- and 7-(α-thienyl)dihydro-1,2,4-triazolo[1,5-a]pyrimidines. The tautomer composition of synthesized compounds was analyzed.*

A convenient method for the preparation of dihydroazolopyrimidines containing angular nitrogen atom entails the cyclocondensation of aminoazoles with unsaturated aromatic ketones [2,3]. Most 5,7-diaryldihydro-1,2,4-triazolo[1,5-*a*]pyrimidines in solution and in the solid phase exist as the enamine 4,7-dihydro form, while relative stabilization of imine forms and formation of tautomer mixtures in solution is observed when electron-donor aromatic substituents are present in the dihydropyrimidine system [3, 4]. In the present work, we synthesized and studied the tautomeric equilibrium in series of 5- and 7-(α-thienyl)triazolopyrimidines.




II–V a R = H, b R = $CH_3$, c R = $CH_3O$,
d R = $(CH_3)_2N$, e R = Cl, f R = Br

* For communication 5, see [1].

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TABLE 1. Characteristics of Compounds IVa,b,e,f, and Va-f

| Compound | Empirical formula | Found, % / Calculated, % N | mp, °C | IR spectrum (KBr), $\nu_{C=C}$, $cm^{-1}$ | UV spectrum (izopropanol), $\lambda_{max}$, nm ($\varepsilon \cdot 10^{-3}$) | Yield, % |
|---|---|---|---|---|---|---|
| IVa | $C_{15}H_{12}N_4S$ | 20,2 / 20,0 | 201...202 | 1665 | 284 (3,9) | 40 |
| IVb | $C_{16}H_{14}N_4S$ | 19,1 / 19,0 | 193 | 1665 | 282 (3,9) | 40 |
| IVc | $C_{15}H_{11}ClN_4S$ | 17,8 / 17,8 | 212...213 | 1660 | 288 (4,5) | 30 |
| IVd | $C_{15}H_{11}BrN_4S$ | 15,5 / 15,6 | 218 | 1660 | 288 (4,4) | 60 |
| Va | $C_{15}H_{12}N_4S$ | 20,0 / 20,0 | 186...188 | 1650 | 298 (4,3) | 65 |
| Vb | $C_{16}H_{14}N_4S$ | 19,1 / 19,0 | 215...217 | 1660 | 299 (4,4) | 10 |
| Vc | $C_{16}H_{14}N_4OS$ | 18,3 / 18,1 | 218...220 | 1670 | 296 (5,1) | 15 |
| Vd | $C_{17}H_{17}N_5S$ | 21,6 / 21,7 | 213...214 | 1650 | 298 (4,8) | 10 |
| Ve | $C_{15}H_{11}ClN_4S$ | 17,7 / 17,8 | 230...231 | 1660 | 299 (4,5) | 35 |

Compounds IVa,b,e,f, and Va-e were obtained by the condensation of 3-amino-1,2,4-triazole (I) with thiophene analogs of chalcone II and III by heating equimolar amounts of the starting reagents in dimethylformamide at reflux for 10-15 min. Significantly lower yields were obtained for the products of the reaction of amine I with ketones II and, especially, III than for the products of the analogous condensations using 1,3-diarylpropenones (chalcones) [2]. Considerable amounts of the starting reagents are detected in the reaction mixture by thin-layer chromatography even after 20-30 min reaction. The yields of the condensation products could not be improved by increasing the reaction time due to considerable tar formation.

The IR spectra of IV and V taken in KBr pellets contain strong stretching bands for the –NH–C=C– fragment at 1650-1670 $cm^{-1}$, typical for 1,4-dihydroazine systems [5] and indicates the enamine structure (A) for these compounds in the solid phase. The electronic absorption spectra of IVa,b,e,f, and Va-f in 2-propanol are analogous to the spectra of other 4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidines [2, 4] and show a weak band at 282-299 nm. The lack of absorption at longer wavelengths indicates, in accord with our previous work [2, 6], the absence of imine form B in solutions in 2-propanol.

PMR spectroscopy provides the greatest information on the equilibrium tautomeric composition of compound IV and V in solution (Table 2). The PMR spectra show signals for the protons of the =C–CH– fragment of the dihydro form A or the –CH–$CH_2$ fragment of imine form B in addition to the aromatic proton multiplets. When a mixture of tautomers is formed, we also find doubling of the signals for the protons of substituent R (in compounds IVb, Vb-d) and 2-H of the thiazole ring. Comparison of the integral intensities of the corresponding signal groups permits us to determine the tautomer composition of the obtained compounds in solutions (see Table 2). Analysis of these results reveals the relative stabilization of the imine tautomers B of V in comparison to their 5-phenyl-7-(R-phenyl) analogs [2], which exist only as dihydro forms A in $CDCl_3$ and DMSO-$d_6$ (within the sensitivity of PMR detection). This phenomenon should be attributed primarily to the $\pi$-electron-donor effect of the $\alpha$-thienyl substituent since it may be conjugated with the electron-withdrawing azomethine group and triazole fragment.

The shift of the tautomeric equilibrium toward the NH form in proton-withdrawing solvents (DMSO and DMF relative to $CDCl_3$) typical for dihydroazines and their heterofused analogs is attributed to formation of NH···Sol hydrogen bonds [5, 7]. This effect is also seen in solutions of IVb,e,f, and Ve. The opposite effect of the solution nature on the tautomeric composition in the case of Va-d is related, in our view, to nonspecific solvation effects. The significant dependence of the tautomeric composition of V on the nature of substituent R, which cannot be attributed to the electronic effect of this substituent, was demonstrated analogously.

TABLE 2. Chemical Shifts of the Protons of Tautomers A and B of IVa,b,e,f, and Va-e,* δ, ppm

| Compound | Solvent | Tautomer | 2-H (1H, s) | 6-H*[2] (1H) | 7-H* (1H) | NH (1H, s) | $CH_3$ (3H, s) | Tautomer content, % |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| IVa | DMF-$d_7$ | A | 7,71 | 5,36 d | 6,30 d | 10,2 | — | 100 |
| | $CDCl_3$ | A | 7,32 | 5,14 d | 6,42 d | 11,2 | — | 100 |
| IVb | DMF-$d_7$ | A | 7,74 | 5,41 d | 6,64 d | 10,1 | 2,42 | 100 |
| | $CDCl_3$ | A | 7,35 | 5,11 d | 6,41 d | 11,1 | 2,34 | 90 |
| | | B | 8,02 | $H_A$: 3,64 dd; $H_B$: 3,50 dd | 5,87 dd | — | 2,42 | 10 |
| IVe | DMF-$d_7$ | A | 7,73 | 5,48 d | 6,66 d | 10,3 | — | 100 |
| | $CDCl_3$ | A | 7,30 | 5,41 d | 6,41 d | 11,1 | — | 90 |
| | | B | 8,02 | $H_A$: 3,50 dd; $H_B$: 3,55 dd | 5,86 dd | — | — | 10 |
| | $CDCl_3$ | A | 7,31 | 5,14 d | 6,42 d | 11,1 | — | ~95 |
| | | B | 8,04 | $H_A$: 3,82 dd; $H_B$: 3,89 dd | 5,90 dd | — | — | ~5 |
| Va | DMF-$d_7$ | A | 7,71 | 5,36 d | 6,31 d | 10,2 | — | 50 |
| | | B | 8,02 | $H_A$: 3,89 dd; $H_B$: 3,95 dd | 5,98 dd | — | — | 50 |
| | $CDCl_3$ | A | 7,32 | 5,14 d | 6,11 d | 10,8 | — | 70 |
| | | B | 8,00 | $H_A$: 3,57 dd; $H_B$: 3,40 dd | 5,58 dd | — | — | 30 |

TABLE 2 (continued)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| Vb | DMF-$d_7$ | A | 7,63 | 5,30 d | 6,20 d | — | 2,30 | 50 |
| | | B | 8,01 | $H_A$: 3,81 dd; $H_B$: 3,92 dd | 5,87 | | — | 50 |
| | $CDCl_3$ | A | 7,45 | 5,13 d | 6,07 d | 10,9 | 2,28 | ~95 |
| | | B | 8,01 | $H_A$: 3,42 dd; $H_B$: 3,51 dd | 5,52 dd | — | —*[2] | ~5 |
| Vc | DMF-$d_7$ | A | 7,64 | 5,29 d | 6,19 d | | 3,79 | 40 |
| | | B | 8,03 | $H_A$: 3,81 dd; $H_B$: 3,93 dd | 5,86 dd | — | 3,78 | 60 |
| | $CDCl_3$ | A | 7,5 | 5,13 d | 6,05 d | 10,7 | 3,73 | 100 |
| Vd | DMF-$d_7$ | A | 7,60 | 5,26 d | 6,11 d | | 2,90 | 40 |
| | | B | 8,02 | $H_A$: 3,87 dd; $H_B$: 3,91 dd | 5,76 dd | — | 2,89 | 60 |
| | $CDCl_3$ | A | 7,45 | 5,14 d | 6,01 d | 10,5 | 2,88 | 100 |
| Ve | DMF-$d_7$ | A | 7,68 | 5,32 d | 6,30 | — | — | 40 |
| | | B | 8,00 | $H_A$: 3,87 dd; $H_B$: 3,95 dd | 5,93 | — | — | 60 |
| | $CDCl_3$ | A | | 5,10 d | 6,07 d | 10,5 | — | 30 |
| | | B | 7,87 | $H_A$: 3,56 dd; $H_B$: 3,35 dd | 5,56 dd | — | — | 70 |

* The aromatic protons of IVa,b,e,f, and Va-f resonate at 7.0-8.1 ppm.

*[2] Coupling constants for tautomers A: $J_{67}$ = 3.0-3.6 Hz, for tautomers B: $J_{AB}$ = -17.5 to -18.2 Hz, $J_{7A}$ = 6.2-7.0 Hz, $J_{7B}$ = 7.3-8.1 Hz.

## EXPERIMENTAL

The IR spectra of IV and V were recorded on a Specord IR-75 spectrophotometer for KBr pellets and the UV spectra were taken on a Specord M-40 spectrometer for $(2\text{-}4)\cdot10^{-5}$ mol/l solutions in 2-propanol. The PMR spectra were taken on a Varian VXR-300 spectrometer for IVa,b,e,f, Va,b and on a Bruker WP-200 spectrometer for Vc-f using TMS as the internal standard. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates using ethyl acetate as the eluent.

**5-Phenyl-7-α-thienyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (IVa).** Solution of 3-amino-1,2,4-triazole I (0.85 g, 10 mmol) and 1-phenyl-3-α-thienyl-2-propen-1-one IIa (2.14 g, 10 mmol) in 0.5 ml of DMF was refluxed for 10 min. Then, 30 ml of acetone were added and 1.1 g (40%) of compound IVa was filtered off; mp 201-202°C.

Compounds IVb,e,f, and Va-e were obtained analogously.

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