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Synthesis of 1,4-Dihydropyrano[2,3-*c*]pyrazole Derivatives

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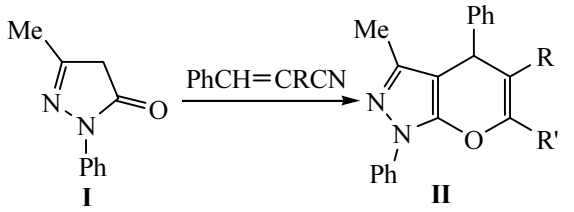
Abstract—In reaction of 2-(2-thienyl)- and 2-(2-furyl)acrylonitriles with 3-methyl-1-phenyl-5-pyrazolone in the presence of basic catalysts 4-thienyl- and 4-furyl derivatives of 3,5-dimethyl-1,7-diphenyl-4,8-dihydropyrano-[2,3-*c*, 5,6-*c*]dipyrazole were obtained.

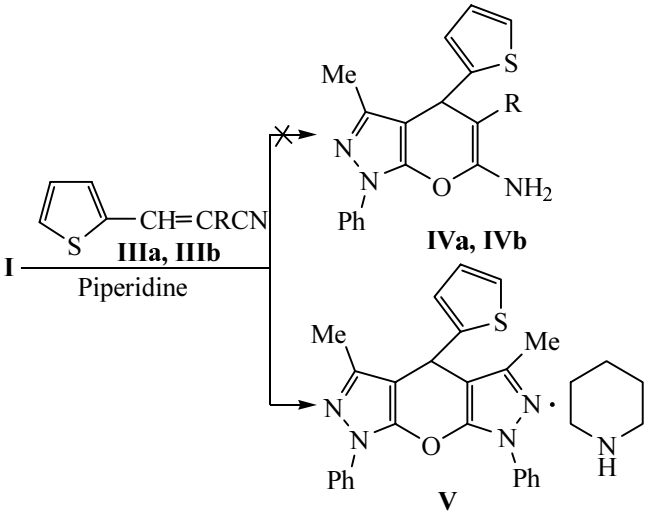
Reactions of 3-methyl-1-phenyl-5-pyrazolone (**I**) with 1-cyano- and 1-ethoxycarbonyl-2-phenylacrylonitrile afforded in high yields 1,4-dihydropyrano[2,3-*c*]pyrazole (**II**) derivatives [1–3].



R = CN, COOEt; R' = NH_2, OH.

Compounds of this series attract interest because of possible pharmacological activity [2]. It is expedient to synthesize analogous derivatives of pyrano[2,3-*c*]pyrazole with thiophene or furan fragments attached to the pyran ring instead of a phenyl substituent.

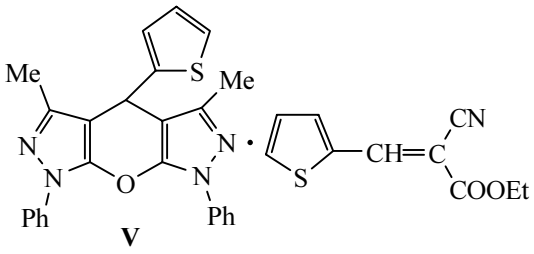
In reactions of compound **I** with acrylonitrile derivatives containing a thienyl moiety **IIIa** and **IIIb** we planned to obtain substances **IVa** and **IVb** similar in structure to azole **II**.



R = CN (**a**), COOEt (**b**).

However the analysis of products obtained revealed that both reactions occurred by unexpected route and in the presence of piperidine as catalyst furnished the same compound, a molecular complex of 4,8-dihydropyrano-[2,3-*c*, 5,6-*c*]dipyrazole (**V**) with a piperidine molecule. This structure was assigned to the compound based on the molecular weight, and also IR and ^{1}H NMR spectra; the composition was confirmed by elemental analysis.

At the use of diethylamine as catalyst the reaction between compounds **I** and **IIIb** gave rise to a complex of the same heterocycle with one molecule of the initial reagent **IIIb**.



On recrystallization of the latter complex from the aqueous alcohol the complex decomposed, and compound **V** was separated in an individual state.

In preparation of furan derivatives we used three known procedures of the synthesis of 1,4-dihydropyrano-[2,3-*c*]pyrazoles: the cyclocondensation of compound **I** with acrylonitriles [1, 2], the reaction of 3-methyl-4-aryl-methylene-5-pyrazolones (**VI**) with malonodinitrile or with cyanoacetic acid ester [4, 5], and the three-component condensation of compound **I** with aromatic aldehydes and malonomononitrile or malonodinitrile [6, 7]. All the three procedures afforded the same product that according to

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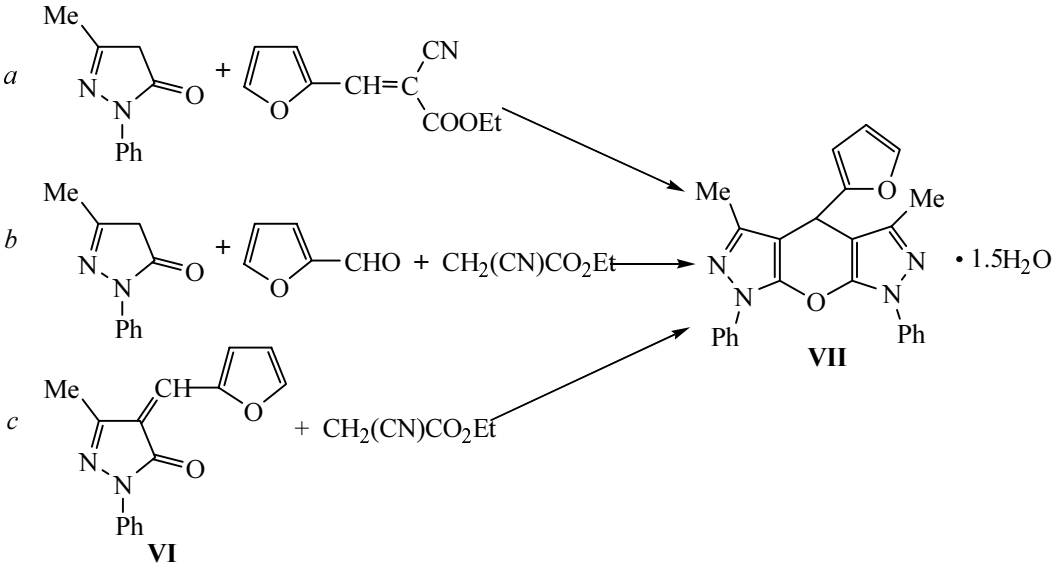
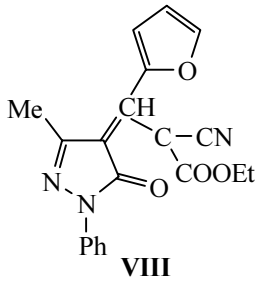


the IR and ^{1}H NMR spectra was assigned structure **VII** similar to that of compound with thiophene moiety.

Inasmuch as compound **VII** lacked a fragment from ethyl cyanoacetate it is presumable that the latter is not involved in the building up of the tricyclic structure. However in the reaction of compound **I** with furfural formed product **VI** that only by treatment with ethyl cyanoacetate was converted into compound **VII**. Apparently the latter compound formed via an intermediate **VIII** notwithstanding which route took the reaction.



VIII

EXPERIMENTAL

The reaction progress was monitored and the purity of compounds obtained was checked by TLC on Silufol plates (eluent chloroform). IR spectra were recorded on a spectrophotometer UR-20 from samples pelletized with KBr. ^{1}H NMR spectra were registered on spectrometer Bruker AC-200 in DMSO-d_6. Molecular weights were measured by reversed ebullioscopy procedure in chloroform on a osmometer 302B device.

Molecular complex of 3,5-dimethyl-4-(2-thienyl)-1,7-diphenyl-4,8-dihydropyrano[2,3-*c*, 5,6-*c*]-dipyrazole (V) with a piperidine molecule. *a*. A mixture of 0.11 g (0.63 mmol) of 3-methyl-1-phenyl-5-pyrazolone (**I**), 0.1 g (0.63 mmol) of 2-(2-thienyl)-1-cyanoacrylonitrile (**IIIa**), and 0.01 ml of piperidine in 4.7 ml of ethanol was stirred for 15 min at 70°C. The solution was evaporated by ~1/3 of its volume, the separated precipitate was filtered off, washed with ethanol, and dried in a vacuum desiccator. Yield 0.1 g (77%), mp 160°C. IR spectrum, cm^{-1}: 960, 1040, 1080, 1120, 1190, 1230, 1290, 1380, 1430, 1500, 1600, 2650, 2750, 2870, 2950. ^{1}H NMR spectrum , δ, ppm: 1.6 s (6H, Pi), 2.2 s (6H, 2Mε), 2.9 s (4H, Pi), 4.8 s (1H, CH), 6.7–7.0 m (3H, thioph.), 7.0–8.0 m (10H, 2Ph). Found, %: C 70.60; H 5.98; N 13.56. *M* 506+10. $C_{30}H_{31}N_5OS$. Calculated, %: C 70.72; H 6.09; N 13.75. *M* 509.

b. A mixture of 0.42 g (2.4 mmol) of compound **I,** 0.5 g (2.4 mmol) of ethoxynitrile **IIIb**, and 0.01 ml of piperidine in 18 ml of ethanol was stirred for 30 min at 70°C. The reaction product was isolated as described in procedure *a*. Yield 0.32 g (63%), mp 160°C. *M* 505+10. No depression of the melting point was observed for a mixture of samples prepared by methods *a* and *b*.

Molecular complex of 3,5-dimethyl-4-(2-thienyl)-1,7-diphenyl-4,8-dihydropyrano[2,3-*c*, 5,6-*c*]dipyrazole (V) with a molecule of 1-ethoxycarbonyl-2-(2-thienyl)acrylonitrile (IIIb). A mixture of 0.42 g (2.4 mmol) of compound **I**, 0.5 g (2.4 mmol) of compound **IIIb**, and 0.02 ml of diethylamine in 18 ml of ethanol was stirred for 30 min at 70°C. The product was isolated as described for the previous synthesis. Yield 0.65 g (78%), mp 135°C (from 50% acetone). IR spectrum, cm^{-1}: 740, 940, 1090, 1210, 1260, 1415, 1510, 1720, 2215, 2950, 3100.

^{1}H NMR spectrum, δ, ppm: 1.4 t (3H, CH_3), 2.3 s (6H, $2CH_3$), 4.3 m (2H, CH_2), 5.1 s (1H, CH), 6.7–8.2 m (6H, thioph.), 7.2–8.0 m (10H, $2C_6H_5$), 8.5 s (1H, CH). Found, %: C 66.36; H 4.45; N 11.01. $C_{35}H_{29}N_5O_3S$. Calculated, %: C 66.56; H 4.60; N 11.09.

3,5-Dimethyl-4-(2-thienyl)-1,7-diphenyl-4,8-dihydropyrano[2,3-*c*, 5,6-*c*]dipyrazole (V). A solution of 0.1 g (0.14 mmol) of the molecular complex of compound **V** with piperidine in 15 ml of 35% ethanol was heated to boiling. On cooling the separated precipitate was filtered off and washed with ethanol. Yield 0.55 g (82%), mp 180°C. IR spectrum, cm^{-1}: 740, 940, 1090, 1210, 1280, 1415, 1510, 1600, 2850. ^{1}H NMR spectrum, δ, ppm: 2.3 s (6H, $2CH_3$), 5.1 s (1H, CH), 6.7–8.0 m (3H, thioph.), 7.2–8.0 m (10H, $2C_6H_5$). Found, %: C 70.66; H 4.80; N 13.19. $C_{25}H_{20}N_4OS$. Calculated, %: C 70.75; H 4.72; N 13.21.

3-Methyl-1-phenyl-4-furfurylidene-5-pyrazolone (VI). In 35 ml of ethanol was dissolved at heating 1 g (5.7 mmol) of compound **I** and 0.47 ml (5.7 mmol) of furfural. One drop of diethylamine was added, and the mixture was stirred for 1 h at 70°C. On cooling the separated precipitate was filtered off and washed with ethanol. Yield 0.6 g (44%), mp 105°C. IR spectrum, cm^{-1}: 760, 800, 980, 1100, 1480, 1500, 1620, 1700. Found, %: C 71.24; H 4.68; N 11.06. $C_{15}H_{12}N_2O_2$. Calculated, %: C 71.43; H 4.76; N 11.11.

3,5-Dimethyl-4-(2-furyl)-1,7-diphenyl-4,8-dihydropyrano[2,3-*c*, 5,6-*c*]dipyrazole (complex with water) (VII). *a*. A mixture of 0.46 g (2.62 mmol) of compound **I,** 0.5 g (2.62 mmol) of 1-ethoxycarbonyl-2-(2-furyl)acrylonitrile, and 0.01 ml of diethylamine in 18 ml of ethanol was stirred for 80 min at 50°C. The solution was evaporated by ~1/3 of its volume, the separated precipitate was filtered off, washed with ethanol, and dried in a vacuum desiccator. Yield 0.43 g (74%), mp 165°C (from 45% ethanol). IR spectrum, cm^{-1}: 810, 880, 1020, 1080, 1200, 1290, 1400, 1510, 1610, 1800, 2940, 3400. ^{1}H NMR spectrum, δ, ppm: 2.2 s (6H, $2CH_3$), 4.9 s (1H, CH), 6.0–6.5 m (3H, furan), 7.0–8.0 m (10H, $2C_6H_5$). Found, %: C 68.65; H 5.30; N 12.48. $C_{25}H_{23}N_4O_3$. Calculated, %: C 68.97; H 5.29; N 12.87.

b. A mixture of 0.99 ml (12 mmol) of furfural and 1.28 ml (12 mmol) of ethyl cyanoacetate in 40 ml of ethanol was heated to 40°C and a solution of 2 g (12 mmol) of compound **I i**n 40 ml of ethanol and 0.1 ml of diethylamine was added. The mixture was stirred at 70°C for 40 min and was left overnight. On the next day the separated precipitate was isolated as described for procedure *a*. Yield 2.1 g (85%), mp 165°C (from 45% ethanol). IR and ^{1}H NMR spectra were identical to those of compound prepared along procedure *a*. No depression of the melting point was observed for a mixture of samples prepared by methods *a* and *b.*

c. A mixture of 1 g (4 mmol) of compound **VI** and 0.64 ml (6 mmol) of ethyl cyanoacetate in 40 ml of ethanol was heated to 40°C, 0.1 ml of diethylamine was added, and the mixture was left standing for 2 h. On the next day the separated precipitate was isolated as described for procedure *a.* Yield 0.6 g (72%), mp 165°C (from 45% ethanol). IR and ^{1}H NMR spectra were identical to those of compounds prepared along procedures *a* and *b.* No depression of the melting point was observed for a mixture of samples prepared by methods *a* and *c* and also *b* and *c.*

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