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AZINES AND THEIR ACYCLIC DERIVATIVES AS TRANSFERERS OF ONE-CARBON FRAGMENT IN REACTIONS WITH PYRAZOLONES

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*Enehydrazine derivatives have been obtained by the reaction of 6-phenyl-1,2,4-triazine 4-oxide with pyrazolones **2**, which on further heating with pyrazolones **2** are converted into the corresponding symmetrical or unsymmetrical derivatives of dipyrazolylmethane. Enehydrazine derivatives of 1,3-dimethyl-5-nitrosouracil and 1,3-dimethylimidazolidine interact with 3-methyl-1-phenyl-5-pyrazolone (**2a**) with the formation of dipyrazolylmethane derivative. On interacting compound **2a** or 3-methyl-1-(p-nitrophenyl)-5-pyrazolone with 3,6-diphenyl-1,2,4-triazine 4-oxide **12** the corresponding 4,4'-bispyrazolones are formed, but the interaction of compound **12** with 3-(p-nitrophenyl)-1-phenyl-5-pyrazolone leads to dipyrazolylmethane derivative. Dipyrazolylmethane derivative is obtained on heating of fervenulin 4-oxide, 2,4-dihydroxy-5-nitropyrimidine, and 1,3,5-triazines: 6-azauracil, 5-azauracil, azacytosine, and 2,4-diamino-s-triazine with pyrazolone **2a**.*

Keywords: azines, pyrazolones, substitution, nucleophilic addition, one-carbon fragment transfer, elimination.

It was shown by us previously that CH-acids interact with 3,6-diphenyl-1,2,4-triazine 4-oxide in the presence of bases with the formation of substitution products at the H-5 atom of the triazine nucleus [1]. It was thereby discovered that such dicarbonyl compounds as acetylacetone or benzoylacetone react in the presence of base by a type of vicarious substitution of hydrogen with the formation of ditriazinylmethane derivative. 5-Indolyl derivatives of 3,6-diphenyl-1,2,4-triazine were obtained by heating 3,6-diphenyl-1,2,4-triazine 4-oxide with indoles in butanol in the presence of trifluoroacetic acid [1]. More recently the preparation of stable σ-adducts [5-(4-hydroxyindol-3-yl)-3,6-diphenyl-4,5-dihydro-1,2,4-triazines] was reported in [2] by the interaction of indoles with 3,6-diphenyl-1,2,4-triazine 4-oxides in methylene chloride in the presence of trifluoroacetic acid. These adducts were announced as intermediates in the nucleophilic substitution of hydrogen in azine N-oxides, It is strange however that the indicated adducts failed to be converted by the authors through dehydration of them into known substitution products*. 6-Phenyl-1,2,4-triazine 4-oxide reacts with CH-acids in the presence of base with opening of the triazine ring at the $C_{(3)}$–$N_{(4)}$ bond with the formation of the corresponding α-hydrazino substituted oximes [4]. For hydrazones of α-hydrazino-substituted oximes a ring–chain isomerism of the

* In the end, by oxidation of the 4-hydroxy derivatives analogously to [3] and deoxidation of the resulting 1-methylindolyl derivative of 3,6-diphenyl-1,2,4-triazine 4-oxide, 5-(1-methyl-3-indolyl)-3,6-diphenyl-1,2,4-triazine, described previously in [1], was obtained by the authors of [2].

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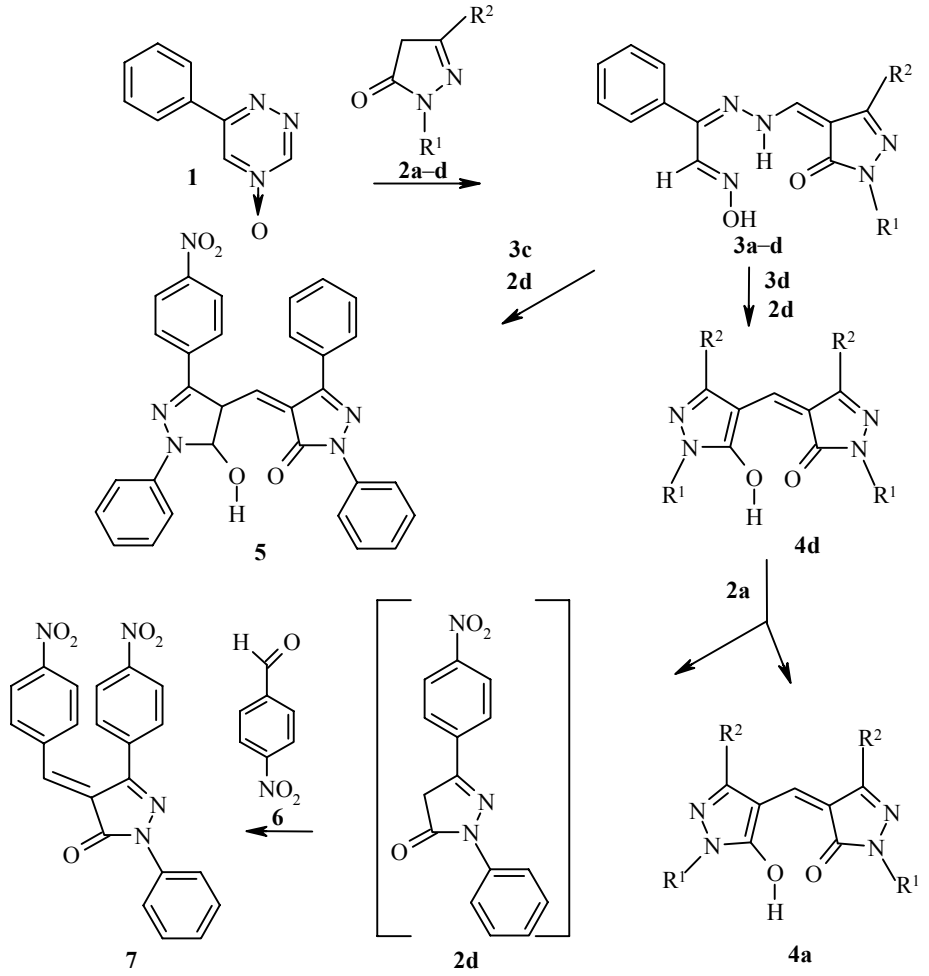
hydrazone – 1,2,4-triazine 4-oxide type is possible in principle. A similar tautomerism for hydrazones of *E*-isomers of α-hydrazino-substituted oximes was described in [5]. Heterocyclization of 1,2-diketone *Z*-hydrazone-*E*-oxime derivatives to 1,2,4-triazine 4-oxides and the tautomeric equilibrium of the latter with 4-hydroxy-1,2,4-triazines was described by German chemists [6]. The corresponding 4-N-oxides were obtained by the oxidation of 4-hydroxy-1,2,4-triazines [3]. Regretably the authors of [7] did not pay attention to publications [3,5,6] and presented results of their investigations on ring–chain tautomerism in a series of 4-hydroxy-1,2,4-triazines without considering the studies mentioned above.

In a preliminary communication [8] we reported that 6-phenyl-1,2,4-triazine 4-oxide **1** interacts with pyrazolones **2a-d** on heating in butanol in the absence of base with the formation of hydrazine derivatives **3a-d**.



2, **3 a** R^1 = Ph, R^2 = Me; **b** R^1 = $C_6H_4NO_2$-*p*, R^2 = Me; **c** R^1 = R^2 = Ph;
d R^1 = Ph, R^2 = $C_6H_4NO_2$-*p*

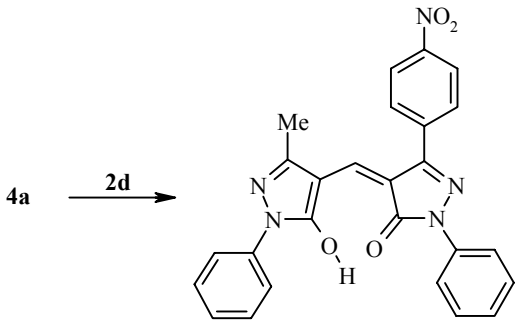
The hydrazine derivatives **3** obtained exist in chloroform solution as acyclic enehydrazines, which are evidently stabilized through the formation of pseudopolycyclic systems involving hydrogen bonds. The structure of this type of compounds has been investigated by us in solution with the aid of ^{1}H NMR [3] and in the crystalline state by X-ray structural analysis [9].

On extended heating of enehydrazines **3** with pyrazolones **2** substitution occurs of both the hydrazine and the carbonyl fragments of molecules **3** with the formation of symmetrical **4** or unsymmetrical **5** derivatives of dipyrazolylmethane. On heating hydrazine derivative **3d** with pyrazolone **2d** the corresponding symmetrical derivative of dipyrazolylmethane **4d** was isolated [8].

The unsymmetrical derivative of dipyrazolylmethane **5** was obtained by us on heating enehydrazine **3c** with pyrazolone **2d**. The molecular mass of compound **5**, determined mass-spectrometrically, corresponds with that calculated for the proposed structure. It is evident that the formation of compound **5** occurs as a result of substitution of hydrazine residue of the compound **3c** molecule.

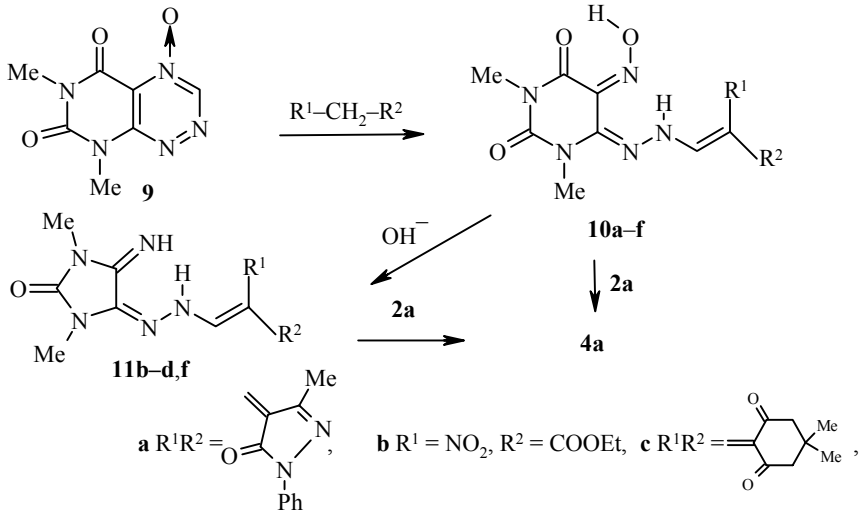
It is interesting that dipyrazolylmethane derivative **4a** is formed in 50-55% yield on heating the other symmetrical derivative **4d** with pyrazolone **2a**. After removing of compound **4a** by treating the mother liquor of the reaction mass with *p*-nitrobenzaldehyde **6**, *p*-nitrobenzylidene derivative of pyrazolone **7** was obtained. This indicates the displacement of the residue of pyrazolone **2d** from the molecule **4d** in unchanged form.

It should be noted that under analogous conditions derivative **4a** reacts with a twofold excess of pyrazolone **2d** with the formation of only a small quantity of unsymmetrical derivative **8**.

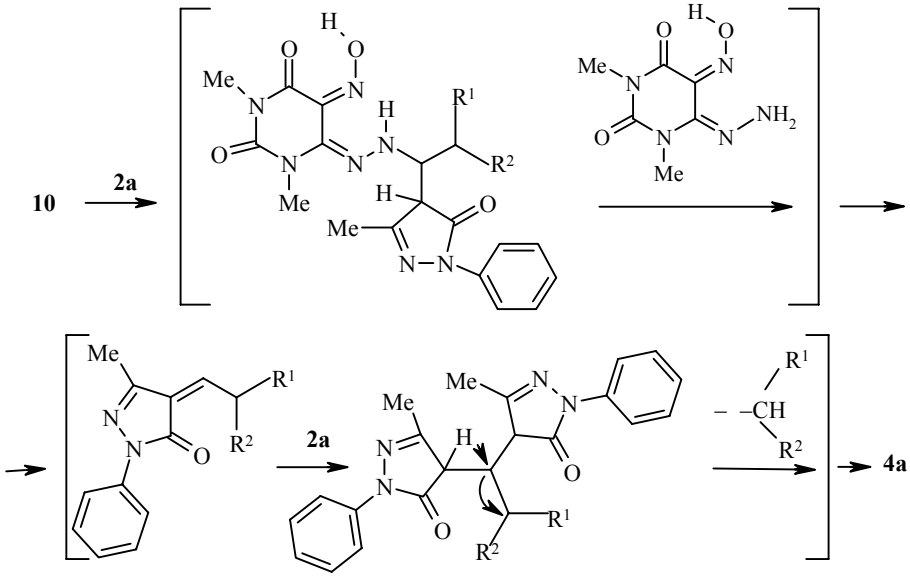


The structure of certain derivatives of dipyrazolylmethane has been studied previously using ^{1}H NMR and IR spectroscopy. It was shown that these compounds exist as *Z-s-cis*-isomers with a central H-bonded eight-membered ring [10]. Later an X-ray structural analysis was carried out on crystals of 4,4'-methylenebis(3-methyl-1-phenyl-5-pyrazolone) **4a** and it was established that the compound **4a** molecule was symmetrical about the axis passing through $C_{(1)}$ and the H-bonded atoms. The central H-bonded eight-membered ring has a coplanar disposition of the non-hydrogen atoms. The hydrogen atom is situated in the middle of the distance between the oxygen atoms of the pyrazole fragments [3].

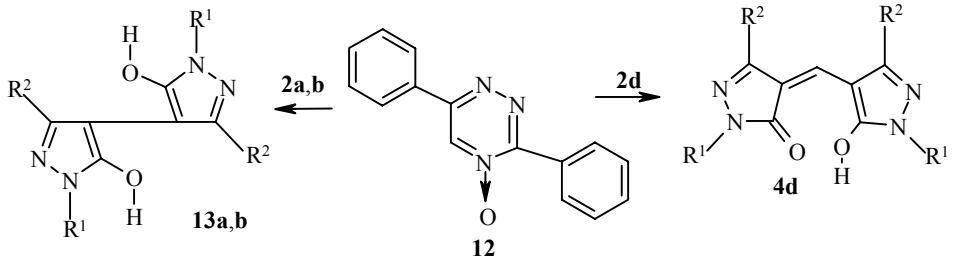
Fervenulin 4-oxide **9** reacts with pyrazolones **2** analogously to 6-phenyl-1,2,4-triazine 4-oxide **1**. On interacting compound **9** with CH-acids in DMSO in the presence of base enehydrazine derivatives **10** were obtained [11], which on heating with pyrazolone **2a** are converted into the known dipyrazolylmethane **4a**.



The enehydrazine derivatives of 1,3-dimethyluracil **10b-d,f** are decomposed by aqueous alkali to the corresponding enehydrazine derivatives of imidazolidines **11**. Enehydrazines **11** also react with pyrazolone **2a** with the formation of the known dipyrazolylmethane **4a** (from compound **11b** 20, **11c** 70, and **11d** 50%). It is evident that the formation of compound **4a** is possibly a result of sequential stages of nucleophilic addition of pyrazolone **2a** at the double bond of the enehydrazine fragment of compound **10** (or **11**) and subsequent decomposition of the adducts with substitution of both the hydrazine and carbonyl residues according to the scheme.



Pyrazolones **2** react with 3,6-diphenyl-1,2,4-triazine 4-oxide **12** in another way. As a result of the reaction in this case, depending on the nature of the nucleophile, either oxidative dimerization of pyrazolones or the formation of the corresponding dipyrazolylmethane is observed. In the case of the reaction of oxide **12** with pyrazolone **2d** dipyrazolylmethane **4d** is formed, but in the case of compound **2a,b** bispyrazolones **13a,b** are formed.

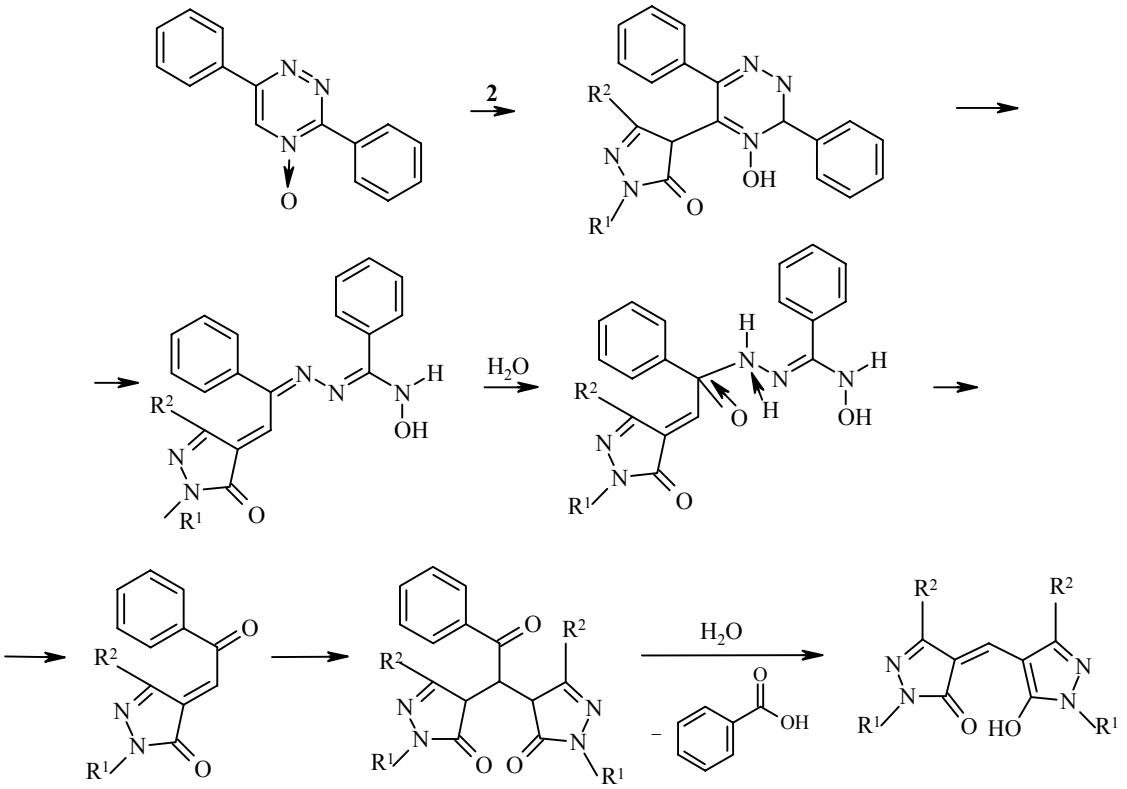


a R^1 = Ph, R^2 = Me, **b** R^1 = $C_6H_4NO_2$-*p*, R^2 = Me, **d** R^1 = Ph, R^2 = $C_6H_4NO_2$-*p*

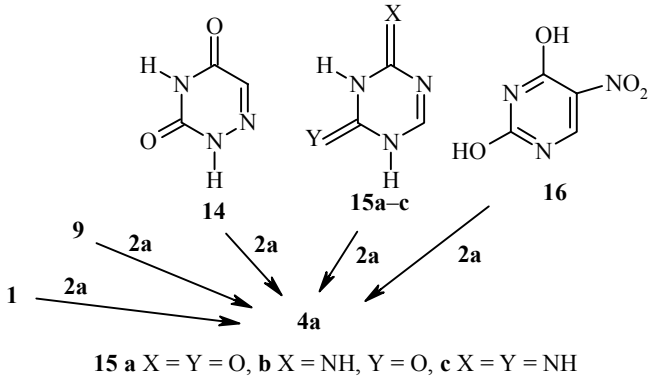
The molecular mass of compound **13** determined mass spectrometrically, corresponded to that calculated. In the ^{1}H NMR spectra of compound **13** there were signals of the protons of all the groups in agreement with the structure proposed.

It must be noted that the reaction of compound **12** with pyrazolone **2d** proceeds significantly more slowly than the analogous reaction of pyrazolone **2** with compound **1**.

The difference in the rates of conversion of 1,2,4-triazine 4-oxides **1** and **12** may be caused by the difference in the mechanisms of breakdown of the intermediate $C_{(3)}$ and $C_{(5)}$ adducts. As is seen from the proposed scheme the transformation of triazine **1** with pyrazolones occurs as a result of decomposition finally of two C–N bonds ($C_{(3)}$–$N_{(2)}$ and $C_{(3)}$–$N_{(4)}$) of the triazine ring. At the same time fission of a C–N bond ($N_{(4)}$–$C_{(5)}$) and C–C bond ($C_{(5)}$–$C_{(6)}$) is necessary for the transformation of triazine **12** into derivatives of dipyrazolylmethane.

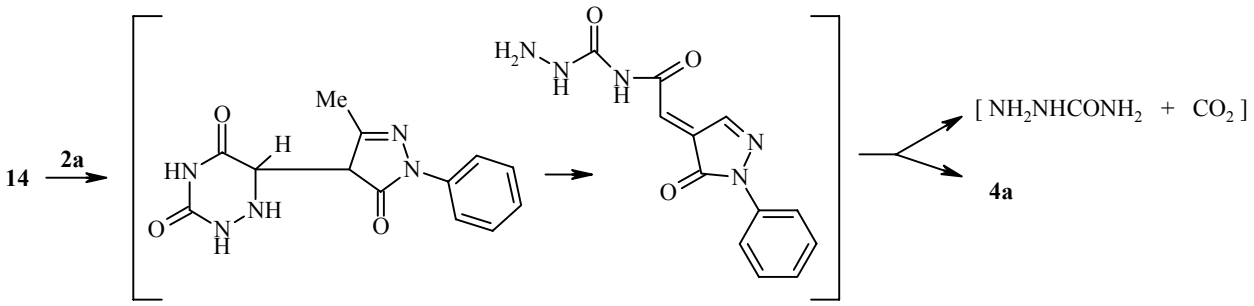


In the course of further work it was established that other azines also react with pyrazolone **2a** with the formation of dipyrazolylmethane derivative **4a**. In the case of the reaction of 6-azauracil **14** as well as of 1,3,5-triazine derivatives (5-azauracil **15a** [12], azacytosine **15b** [13], and 2,4-diamino-1,3,5-triazine **15c**) with pyrazolone **2a**, product **4a** was isolated. The formation of compound **4a** was also observed by us in the present work on interaction of pyrazolone **2a** with 2,4-dihydroxy-5-nitropyrimidine **16**.

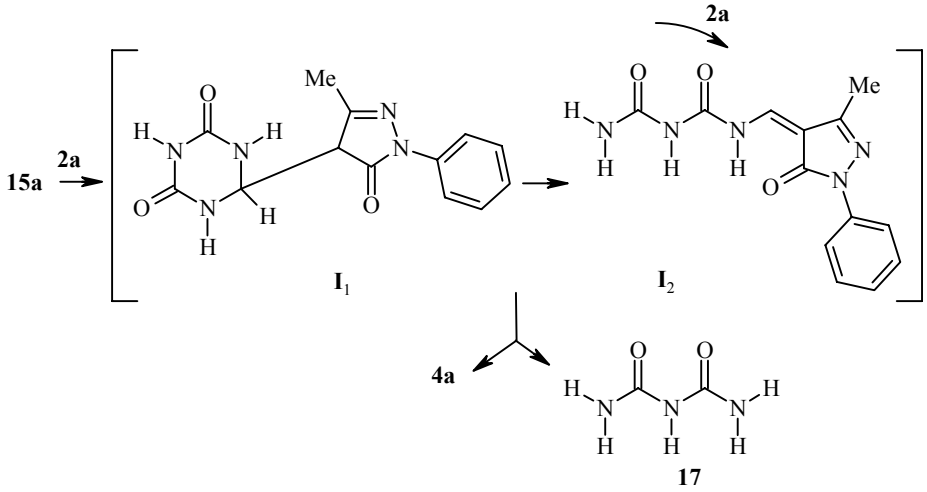


15 a X = Y = O, **b** X = NH, Y = O, **c** X = Y = NH

The formation of dipyrazolylmethane **4a** when converting 6-azauracil **14** may be represented as a sequence of steps. There is first a nucleophilic attack at the $C_{(6)}$ carbon atom, opening of the triazine ring, fission of the C–N bond, a second nucleophilic attack, and then transformation of the resulting intermediate to the final products according to the scheme.



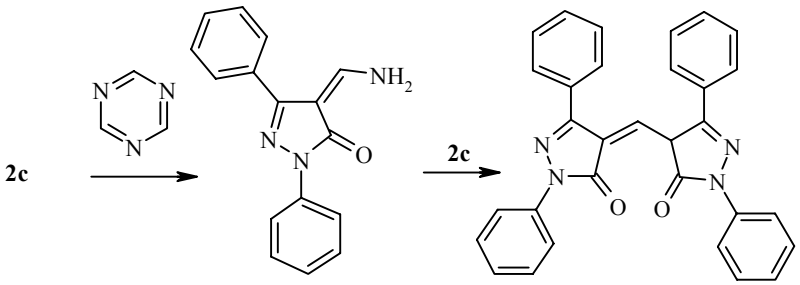
The mechanism of the transformation of 1,3,5-triazines **15** by pyrazolones **2** may be illustrated using as example the conversion of 1,3,5-triazine **15a** described by us in a short communication [12].



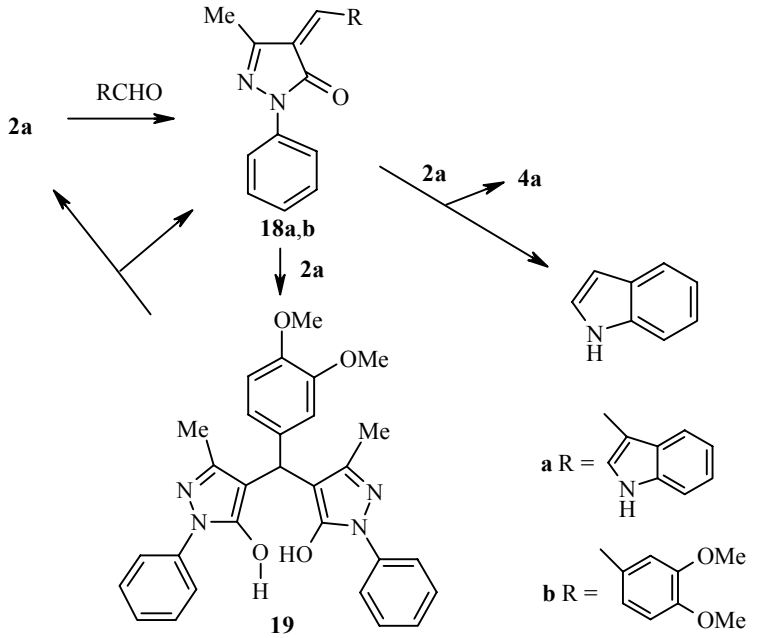
The formation of dipyrazolylmethane **4a** probably occurs through the stage of forming intermediate $\mathbf{I_1}$ as a result of nucleophilic addition of pyrazolone **2a** at the $C_{(6)}$ atom of azauracil **15a**.

Fission of the $C_{(6)}$–$N_{(1)}$ (or $C_{(6)}$–$N_{(5)}$) bond then occurs with subsequent attack of intermediate $\mathbf{I_2}$ by second molecule of pyrazolone with the formation of products **4a** and **17**. The formation of biuret **17** in the reaction confirms the fact that the first nucleophilic attack occurs at the $C_{(6)}$ atom of 5-azauracil.

A similar mechanism to form dipyrazolylmethanes probably takes place in the reaction of unsubstituted 1,3,5-triazine with 1,3-diphenyl-5-pyrazolone [14].



It is interesting that 3-methyl-1-phenyl-5-pyrazolone **2a** interacts with the model methylidene **18a** with the formation of the known dipyrazolylmethane **4a** and unsubstituted indole [15].



A similar reaction of transfer of an one-carbon fragment also probably takes place in the interaction of 3-formyl-2-methylindole with an excess of pyrazolone **2a** [16]. Dipyrazolylmethane **4a** and 2-methylindole are formed as a result of this reaction.

The arylidene derivative **18b** reacts with pyrazolone **2a** under analogous conditions with the formation of colorless dipyrazolylarylmethane **19**, which is converted into the initial substance **18** on recrystallization from acetic acid [17].

On the whole it is evident that the conversions of di- and triazines described may be considered as part of the multistage transformations of these compounds by pyrazolones, which is of interest for understanding the mechanisms. It is interesting that azines, their cyclic or acyclic adducts, essentially play the role of donor, and the pyrazolones that of acceptor, of the one-carbon –CH= fragment. Substitution (or resubstitution) of hydrazine and carbonyl fragments of enehydrazines (enamines) probably occurs through the stage of forming intermediate adducts of the type of the model arylpyrazolylmethanes **19**. The stages of adding pyrazolones at the double bond of enehydrazines are analogous to the Michael reaction.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WH 90 (90 MHz) impulse spectrometer. Mass spectra were obtained on a Finnigan MAT 8200 instrument under standard conditions.

Synthesis of Enehydrazine Derivatives of Imidazolidine 11. The appropriate compound **10** (0.3 mmol) was stirred for 45-50 min in 5% aqueous NaOH solution (5 ml). The reaction mixture was acidified to pH 4-5 with concentrated HCl. The solid was filtered off and recrystallized from ethanol. Compound number, mp °C, and yields, % were: **11b**, 132-133, 45-50; **11c**, 222-223, 55-60; **11d**, 189-190, 50-55; **11f**, 144-156, 40-45.

Reaction of Enehydrazine Derivatives of 1,3-Dimethyl-5-nitrosouracil 10 with Pyrazolone 2a. The appropriate enehydrazine **10** (0.5 mmol) in butanol (3 ml) was boiled with pyrazolone **2a** (1.0 mmol) for 10 h. The reaction mixture was cooled, the solid **4a** was filtered off, and recrystallized from aqueous DMF. The yields of compound **4a** were: from **10a** – 50, **10b** – 65, **10c** – 80, and **10d** – 60%.

Reaction of Enehydrazine Derivatives of 1,3-Dimethylimidazolidines 11 with Pyrazolone 2a was carried out analogously to the reaction of compound **10** with **2a**. Yield of compound **4a** from **11b** was 20, **11c** – 70, **11d** – 50%.

Reaction of 3,6-Diphenyl-1,2,4-triazine 4-Oxide 12 with Pyrazolones 2. A. Compound **12** (0.125 g, 0.5 mmol) was boiled with pyrazolone **2a** (0.174 g, 1.0 mmol) in butanol (3 ml) for 3 h. Solid **13a** was filtered from the hot reaction mixture. Yield 0.070 g (28%); mp >300°C. Mass spectrum, *m/z* 346 $[M]^+$. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.15 (3H, s, CH_3); 7.15-7.30 (1H, m, 4-H arom.); 7.45-7.55 (2H, m, 3-, 5-H arom.); 7.65-7.80 (2H, m, 2-, 6-H arom.); 11.3 (1H, br. s, OH).

Reaction of Compound 12 with Pyrazolone 2b was carried out analogously. Yield of compound **13b** 0.020 g (18%); mp >300°C. Mass spectrum, *m/z* 436 $[M]^+$.

B. Compound **12** (0.5 mmol) was boiled in butanol (3 ml) with pyrazolone **2d** (0.5 mmol) for 3 h. Solid **4d** was filtered off from the hot reaction mixture. Yield 0.010 g (3.5%).

Reaction of 6-Azauracil 14 with Pyrazolone 2a. 6-Azauracil **14** (0.2 g, 1.75 mmol) and pyrazolone **2a** (0.6 g, 3.5 mmol) were boiled in butanol (12 ml) for 6 h. The reaction mixture was cooled, and unreacted starting material (0.12 g) was filtered off. The mother liquor was evaporated under vacuum, and the solid residue was recrystallized from aqueous DMF. Compound **4a** (0.01 g, 4%) was obtained.

Reaction of 2,4-Diamino-1,3,5-triazine 15c with pyrazolone 2a. Compound **15c** (0.222 g, 2.0 mmol) and pyrazolone **2a** (0.7 g, 4.0 mmol) were boiled in butanol (10 ml) for 6 h. The precipitated solid was filtered off and recrystallized from aqueous DMF. Compound **4a** (0.086 g, 12%) was obtained.

Reaction of 2,4-Dihydroxy-5-nitropyrimidine 16 with Pyrazolone 2a. 2,4-Dihydroxy-5-nitropyrimidine **16** (0.125 g, 1.0 mmol) and compound **2a** (0.358 g, 2.0 mmol) were boiled in butanol (3 ml) for 5 h. Solid **4a** was filtered from the hot reaction mixture. Yield 0.109 g (31%).

Synthesis of Pyrazolidones 18a,b. Pyrazolone **2a** (6.0 mmol) was boiled with the appropriate aldehyde (6.0 mmol) in ethanol (15 ml) for 1 h. Solid **18** was filtered off and recrystallized. Yield of compound **18a** 75%; mp 239-240°C (DMF). Yield of compound **18b** 40%; mp 160-161°C (ethanol).

Reaction of Compound 18a with Pyrazolone 2a. Methylidene **18a** (0.200 g, 0.66 mmol) was boiled with pyrazolone **2a** (0.24 g, 1.36 mmol) for 7 h. The reaction mixture was cooled, and the precipitate of compound **4a** was filtered off. Yield 0.153 g (65%). The reaction mixture was evaporated to dryness under vacuum. The solid residue was stirred in 5% aqueous NaOH solution (5 ml), the solid indole was filtered off, and recrystallized from ethanol. Yield 0.010 g (13%).

Reaction of Compound 18b with Pyrazolone 2a. Pyrazolidone **18b** (0.322 g, 1.0 mmol) was boiled with pyrazolone **2a** (0.174 g, 1.0 mmol) in ethanol (10 ml) for 2 h. The reaction mixture was cooled, the solid filtered off, and washed with ethanol (10 ml). Compound **19** (0.320 g: 65%) was obtained; mp 185-186°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.31 (6H, s, 2 × CCH_3); 3.69 (3H, s, OCH_3); 3.72 (3H, s, OCH_3); 4.80 (1H, s, CH); 6.70-7.80 (13H, m, H arom.); 11.5 (1H, br. s, OH); 13.70 (1H, br. s, OH). On recrystallizing compound **19** from aqueous acetic acid pyrazolidone **18b** was obtained in 75% yield.

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