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STUDY OF THE REACTION OF 3,5-DIAMINO-4-CARBOMETHOXYPYRAZOLE WITH ACETOACETIC ESTER. SYNTHESIS OF PYRAZOLO[1,5-*a*]PYRIMIDINE

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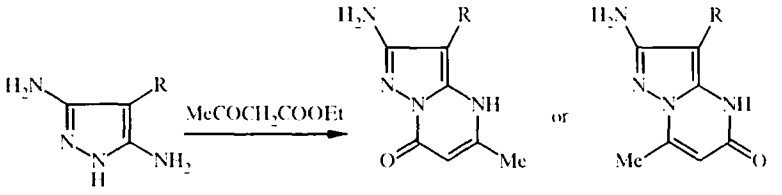
X-Ray structural analysis has shown that condensation of 3,5-diamino-4-carbomethoxypyrazole with acetoacetic ester occurs to give derivatives of 7-oxopyrazolo[1,5-a]pyrimidine (rather than 5-oxo as proposed previously).

Keywords: carbomethoxypyrazole, acetoacetic ester, pyrazolopyrimidine, X-ray structural analysis.

The reaction of 3,5-diamino-4-nitropyrazole (**1**) with β-dicarbonyl compounds has been studied before [1-3]. The subject of our current work is the reaction of 3,5-diamino-4-carbomethoxypyrazole (**2**) [4] with acetoacetic ester. The evidence [5] that the corresponding 4-carbethoxy derivative **3** reacts with acetoacetic ester to give not 7-oxopyrazolopyrimidine (A) but the corresponding 5-oxo derivative (B) contradicts the results obtained by us based on nitropyrazole **1** and, hence, the scheme proposed for this type of cyclization [1].



1, 2, 3 (A), **5** (B), **4**

1 R = NO_2; **2, 4, 5** R = COOMe; **3** (A), (B) R = COOEt

Because of this we decided to determine the correctness of the literature data and to study whether, in fact, exchange of the nitro substituent in position **4** of the pyrazole ring for a carbalkoxy group can change the course of the condensation and cyclization processes. In the first stage of this work we studied the reaction of 3,5-diamino-4-carbomethoxypyrazole (**2**) with acetoacetic ester in methanol in the presence of sodium methylate. In this case the process occurs virtually *via* a single route in 90% yield to give a substance, the structure of which could be the corresponding 5- (**4**) or 7-oxo derivative (**5**). Moreover, according to [5], the structure **4** should be favoured. For an unambigous choice between the structures **4** and **5** we have carried out an isotopic exchange experiment (NH for ND) in their ^{13}C NMR spectra.

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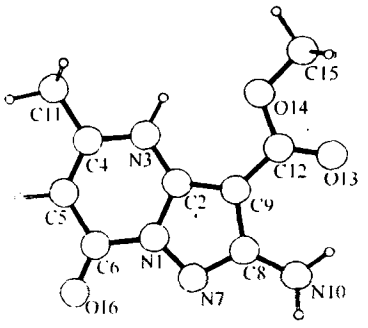
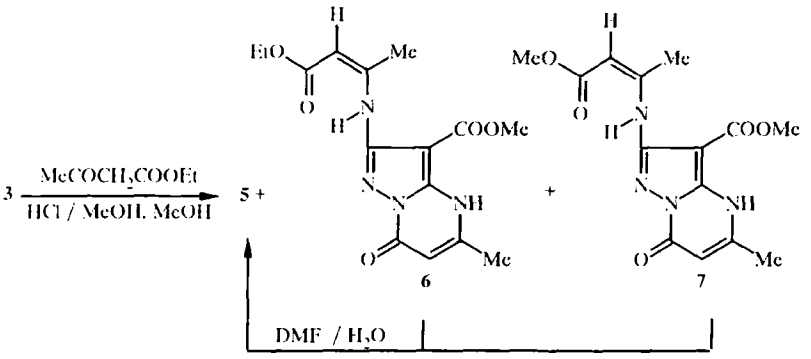


Fig. 1. Numbering of the atoms and structure of compound **5**.

Two drops of a mixture of D_2O and H_2O (distilled) were added to the analyzed solution of the investigated compound, after which the sample was stirred thoroughly and the ^{13}C NMR spectrum recorded. In fact, for the $C_{(5)}$ carbon atom (151.7 ppm) there occurs an isotopic shift of 0.04 ppm to high field through exchange of protons in the NH_2 group for D. At the same time, a similar shift on other carbon atoms in the investigated sample was not found which, evidently, is related to the noticeable mobility of the pyrimidine ring NH proton and the insensitivity (because of this) of neighboring carbon atoms to exchange of a proton for deuterium. No other information from the ^1H and ^{13}C spectra permitted assignment of the structure of the investigated compound to one of these two variants. Hence, to determine exact information in our work, we used X-ray structural analysis (Fig. 1).

The results of the X-ray diffraction analysis have shown that, as in the case of the nitro derivative [1], the reaction occurs to give the 7-oxo bicycle **5** and analysis of the reaction mixture by ^1H NMR spectroscopy shows that no compounds related to **1** to **4** type transformation process are formed in these conditions.

To clear up the dependence of the route of the occurring processes on the reaction conditions used we have studied the reaction of compound **3** with acetoacetic ester in the presence of acid and at heating without catalyst (the latter condition exactly agrees with that studied in [5]).



The reaction of pyrazole with acetoacetic ester in methanol in the presence of hydrochloric acid gave a mixture, all the components of which were identified using ^1H NMR spectroscopy. One of the products of this mixture is compound **5**. Two other compounds (pyrazolylenamines **6** and **7** in the overall ratio **5** to (**6**+**7**) of 1:4) were characterized by the following ^1H NMR spectroscopic signals using DMSO-d_6 solvent: 1.22 (3H, t, $OCH_2\underline{CH_3}$, **6**); 2.31 (6H, s, CH_3, **6**+**7**); 2.46 and 2.48 (two signals, overall 3H, s, ^4J = 0.8 Hz, α-CH_3, **6**+**7**); 3.63 and 3.88 (two signals, 3H, s, $COO\underline{CH_3}$, **6**+**7**); 3.88 (3H, s, $COO\underline{CH_3}$, **7**); 4.12 (2H, q ,$O\underline{CH_2}CH_3$, **6**); 4.87 and 4.89 (two signals, 1H, s, ^4J = 0.8 Hz, β-H, **6**+**7**); 5.80 (2H, s, =CH, **6**+**7**); 11.37 and 11.38 (two signals, 1H, s, NH, **6**+**7**); 11.40 ppm (2H, br. s, NH, **6**+**7**). Acetoacetic ester and methyl ester of acetoacetic acid were present as minor components of the mixture. According to ^1H NMR spectroscopy, heating at 100°C gives an increased content of the bicycle **5** due to hydrolysis of the enamine fragments in compounds **6** and **7** through to full conversion to compound **5**.

TABLE 1. Bond Lengths (Å) in the Structure of Compound **5**

Bond	*d*	Bond	*d*
$N_{(1)}$–$C_{(2)}$	1.421(3)	$C_{(6)}$–$O_{(16)}$	1.250(0)
$N_{(1)}$–$C_{(6)}$	1.452(7)	$N_{(7)}$–$C_{(8)}$	1.318(7)
$N_{(1)}$–$N_{(7)}$	1.366(4)	$C_{(8)}$–$C_{(9)}$	1.506(3)
$C_{(2)}$–$N_{(3)}$	1.393(4)	$C_{(8)}$–$N_{(10)}$	1.334(1)
$C_{(2)}$–$C_{(9)}$	1.383(3)	$C_{(9)}$–$C_{(12)}$	1.411(3)
$N_{(3)}$–$C_{(4)}$	1.383(7)	$C_{(12)}$–$O_{(13)}$	1.247(2)
$C_{(4)}$–$C_{(5)}$	1.392(9)	$C_{(12)}$–$O_{(14)}$	1.371(8)
$C_{(4)}$–$C_{(11)}$	1.492(8)	$O_{(14)}$–$C_{(15)}$	1.438(6)
$C_{(5)}$–$C_{(6)}$	1.430(2)		

Reaction of compound **3** with acetoacetic ester at 160°C without solvent gives a mixture of compounds **5** and **6** in the ratio 15:85. Upon recrystallization of this mixture from DMF which contained water, almost pure bicycle **5** was produced. This, apparently, is the reason that enamine 6 was not commented on by the authors of the study who crystallized it from DMF without investigating the composition of the reaction mixture. It seems likely that enamine hydrolysis occurred and a single substance separated which did not contain an enamine fragment.

To check this hypothesis, a mixture of compounds **5** and **6**, produced in the reaction mixture, was crystallized from specially anhydrous DMF, as a result of which the pure compound **6** was separated and characterized.

Hence, in agreement with the discussed process of pyrimidine cyclization via reaction of 3,5-diamino-4-nitropyrazole with acetoacetic ester [1-3], the predominant route is the formation of 7-oxopyrazolo[1,5-*a*]-pyrimidines.

EXPERIMENTAL

NMR spectra were recorded on an Oxford Unity-400 spectrometer using TMS as internal standard. Mass spectra were obtained on a Finnigan SSQ-700 spectrometer with direct introduction of the sample into the ion source. Monitoring of the purity of the products and the course of the reaction was carried out using TLC on Fluka TLC-Cards Silica gel 60778 plates.

TABLE 2. Bond Angles (deg.) in the Structure of Compound **5**

Angle	ω	Angle	ω
$C_{(6)}$–$N_{(1)}$–$N_{(7)}$	128.52	$N_{(1)}$–$C_{(6)}$–$O_{(16)}$	117.60
$C_{(2)}$–$N_{(1)}$–$N_{(7)}$	110.73	$N_{(1)}$–$N_{(7)}$–$C_{(8)}$	108.35
$C_{(2)}$–$N_{(1)}$–$C_{(6)}$	120.61	$N_{(7)}$–$C_{(8)}$–$N_{(10)}$	126.71
$N_{(1)}$–$C_{(2)}$–$C_{(9)}$	106.91	$N_{(7)}$–$C_{(8)}$–$C_{(9)}$	109.38
$N_{(1)}$–$C_{(2)}$–$N_{(3)}$	120.95	$C_{(9)}$–$C_{(8)}$–$N_{(10)}$	123.85
$N_{(3)}$–$C_{(2)}$–$C_{(9)}$	132.14	$C_{(2)}$–$C_{(9)}$–$C_{(8)}$	104.55
$C_{(2)}$–$N_{(3)}$–$C_{(4)}$	120.17	$C_{(8)}$–$C_{(9)}$–$C_{(12)}$	124.59
$N_{(3)}$–$C_{(4)}$–$C_{(11)}$	118.38	$C_{(2)}$–$C_{(9)}$–$C_{(12)}$	130.84
$N_{(3)}$–$C_{(4)}$–$C_{(5)}$	119.45	$C_{(9)}$–$C_{(12)}$–$O_{(14)}$	113.65
$C_{(5)}$–$C_{(4)}$–$C_{(11)}$	121.05	$C_{(9)}$–$C_{(12)}$–$O_{(13)}$	127.79
$C_{(4)}$–$C_{(5)}$–$C_{(6)}$	124.22	$O_{(13)}$–$C_{(12)}$–$O_{(14)}$	118.54
$N_{(1)}$–$C_{(6)}$–$C_{(5)}$	114.32	$C_{(12)}$–$O_{(14)}$–$C_{(15)}$	114.87
$C_{(5)}$–$C_{(6)}$–$O_{(16)}$	128.04		

X-ray Diffraction Analysis. X-ray diffractions were measured with a Guinier camera ($CuK_{\alpha 1}$ radiation, curved Ge monochromator). The sample was prepared by a special method for levelling of textural effects. The spectra were recorded on film and then read off photodensitometrically in steps of 0.01°. Parameters for the monoclinic unit cell were determined using the ITO indexing program [8]. The $P2_{1/a}$ space group was identified using the extinction rule. The crystal structure was determined by the method described in [7] and refined by the Rietveld method using the MRIA program [9]. Bond lengths and bond angles are given in Tables 1 and 2.

2-Amino-3-carbomethoxy-5-methyl-4,7-dihydropyrazolo[1,5-a]pyrimidin-7-one (5). Solution of sodium methylate (0.34 g, 6.4 mmol) in methanol (5 ml) was added to suspension of 3,5-diamino-4-carbomethoxypyrazole (**2**, 1.0 g, 6.4 mmol) in methanol (30 ml). Ethyl ester of acetoacetic acid (3 ml, 23 mmol) was added to the solution formed. The reaction mass was heated for 1 h, cooled, neutralized with aqueous HCl (10%), and filtered to give 1.3 g (92%) of flocculent white solid; mp >270°C (with decomposition, from DMF). M^+ 222. ^1H NMR spectrum (DMSO-d_6): 2.32 (3H, s, CH_3); 3.78 (3H, s, OCH_3); 5.70 (1H, s, ^4J = 0.8 Hz, 6-H); and 5.94 ppm (1H, br. s, NH). ^{13}C NMR spectrum (DMSO-d_6): 19.2 (CH_3); 51.2 (OCH_3); 83.8 ($C_{(4)}$); 100.0($C_{(6)}$); 143.6 ($C_{(5)}$); 149.8 ($C_{(7)}$); 154.9 ($C_{(9)}$); 157.1 ($C_{(2)}$) and 163.5 ppm (<u>C</u>OOCH$_3$). Found, %: C 48.43; H 4.34; N 24.97. $C_9H_{10}N_4O_3$. Calculated, %: C 48.65; H 4.54; N 25.21.

2'-(1'-Carbethoxyprop-1'-en-2'-yl)amino-3-carbomethoxy-5-methyl-4,7-dihydropyrazolo[1,5-*a*]-pyrimidin-7-one (6). Mixture of pyrazole **2** (1.6 g, 10 mmol) and ethyl ester of acetoacetic acid (1.3 ml, 10 mmol) was heated at 160°C for 8 h. The reaction mixture was cooled, treated with cold ethanol and the solid white material obtained was recrystallized from dry DMF. Yield 2.4 g (66%). M^+ 334. ^1H NMR spectrum (DMSO-d_6): 1.22 (3H, t, OCH$_2$<u>C</u>H$_3$); 2.31 (3H, s, CH_3); 2.46 (3H, s, ^4J = 0.8 Hz, α-CH_3); 3.88 (3H, s, COO<u>CH</u>$_3$); 4.12 (2H, q, O<u>CH</u>$_2$CH$_3$); 4.87 (1H, s, ^4J = 0.8 Hz, β-H); 5.80 (1H, s, =CH); 11.37 (1H, s, NH) and 11.40 ppm (1H, br. s, NH). Found, %: C 54.01; H 5.62; N 16.67. $C_{13}H_{18}N_4O_5$. Calculated, %: C 53.89; H 5.43; N 16.76.

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