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CONDENSATION OF PYRAZOL-5-ONES UNSUBSTITUTED IN THE POSITION 1 WITH β-KETO ESTERS. SYNTHESIS OF PYRANO[2,3-*c*]PYRAZOL-6-ONES

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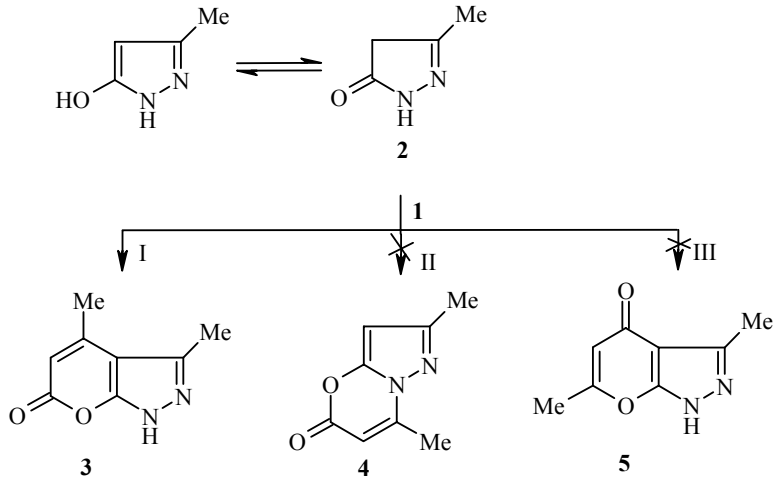
The thermal condensation of β-keto esters and N-unsubstituted pyrazol-5-ones gives good yields of pyrano[2,3-c]pyrazol-6-ones. Other potential routes for the condensation are not realized. The β-diketones react via another scheme to form noncyclic reaction products.

Keywords: pyrazol-5-ones, pyranopyrazol-6-ones, β-keto esters.

We have previously carried out a detailed investigation of the condensation of aminopyrazoles with β-dicarbonyl compounds which gives pyrazolopyridines or pyrazolopyrimidines depending on the structure of the aminopyrazoles [1, 2]. In this work we have studied the potential for 5-hydroxypyrazoles (pyrazol-5-ones) which are unsubstituted in the position 1 to take part in a similar type of condensation.

3,4-Dimethylpyrano[2,3-*c*]pyrazol-6-one (**3**) was prepared for the first time by Wolf [3] by heating 3-methylpyrazol-5-one with an excess of acetoacetic ester. Later, the preparation and some reactions (nitration, chlorination, and bromination) of pyrano[2,3-*c*]pyrazol-6-ones were reported in [4] in which the synthesis of the latter was also carried out using the Wolf method. The authors based this on the use of various pyrazol-5-ones with different substituents in position 1 and only aceto- and benzoylacetic esters as the β-keto esters.



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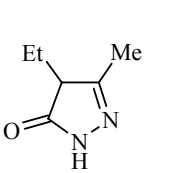
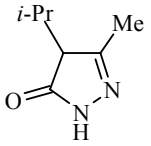
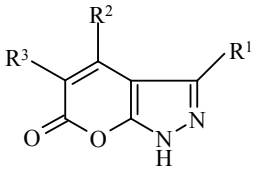
In this work we have studied the behavior of 5-hydroxypyrazoles (pyrazol-5-one) unsubstituted in position 1 with different β-keto esters in similar type condensations. The reaction between acetoacetic ester (**1**) and 3-methylpyrazol-5-one can occur *via* several routes (I, II, or III). Compound **5** is not formed under these conditions. 3,6-Dimethylpyrazol-4-one **5** has been obtained by another scheme. It has different characteristics and its structure has been rigorously proved [5]. The problem of the choice between structures **3** and **4** was resolved by ^{1}H NMR spectroscopic analysis, the condensation product actually corresponding to structure **3**, which is in agreement with data in [3, 4]. For a final proof of this question we attempted to use 4-ethyl-3-methyl- and 4-isopropyl-3-methylpyrazol-5-ones (**6** and **7**) in this condensation. In this case the reaction can only occur *via* route II since position 4 is occupied in both pyrazolones. However, the condensation did not occur and the pyrazolones **6** and **6a** were recovered unchanged from the reaction.



6



6a

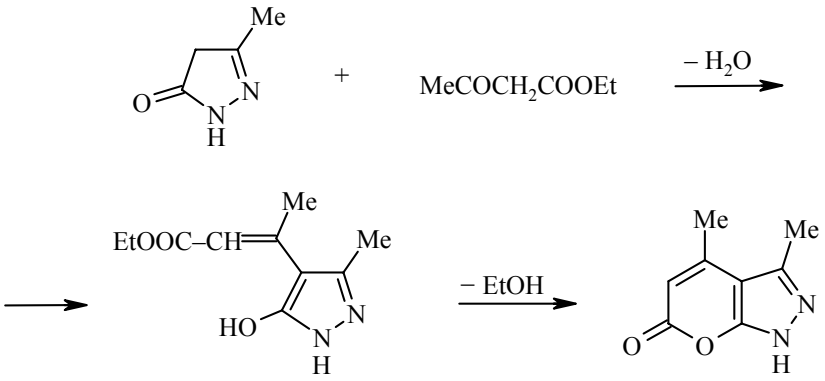


7a–i

7 a $R^1 = R^2 = Me$, $R^3 = H$; **b** $R^1 = R^2 = R^3 = Me$; **c** $R^1 = R^2 = Me$, $R^3 = Et$; **d** $R^1 = R^2 = Me$, $R^3 = n$-Pr; **e** $R^1 = Me$, $R^2 = Ph$, $R^3 = H$; **f** $R^1 = Me$, $R^2 = p$-$MeOC_6H_4$; $R^3 = H$; **g** $R^1 = R^2 = Me$, $R^3 = CH_2COOEt$; **h** $R^1 = Ph$, $R^2 = Me$, $R^3 = H$; **i** $R^1 = p$-$MeOC_6H_4$, $R^2 = Me$, $R^3 = H$

Hence the reaction proceeds with the participation of a free 4 position and oxygen function in the position 5 with the NH group in position 1 being unaffected.

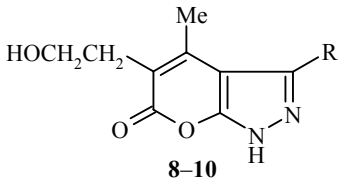
As has been shown [3], the first stage of the reaction is condensation with the separation of water involving the CH_2 group of the pyrazol-5-one. A molecule of alcohol is then lost to form the pyranopyrazol-6-one.



We have used 3-methyl-, 3-phenyl-, and 3-*p*-methoxyphenylpyrazol-5-ones and the acetoacetic, methylacetoacetic, ethylacetoacetic, propylacetoacetic, isopropylacetoacetic, benzoylacetoacetic, *p*-methoxybenzoylacetoacetic, and acetylsuccinic β-keto esters and α-acetylbutyrolactone in the reaction. In all cases the condensation was carried out similarly by heating in a temperature bath at 145-190°C (see Experimental) for 2-4 h to give the products **7a-i**. The yields varied from 20 to 90% (particularly low yields being noted for the benzoylacetic ester). Substituents in the acetoacetic ester markedly decreased the yield and for the isopropylacetoacetic ester it was overall not possible to separate pure material, even though it was present in the mixture according to ^{1}H NMR spectroscopic data. This is evidently connected to the steric hindrance to condensation. The ^{1}H NMR spectra were quite informative. The proton in position 5 of the pyran

ring gave a singlet at 5.8-5.9 ppm with a hyperfine splitting of 1.1 Hz to the neighboring CH_3 group in position 4 which, in turn, occurs as a doublet with J = 1.1 Hz. Hence, for the 5-substituted compounds it is always possible to assign the signal for the CH_3 groups at positions 3 or 4, these occurring side by side at 2.5-2.3 ppm. All of the pyranopyrazoles gave a negative reaction with $FeCl_3$ whereas all of the hydroxypyrazoles gave a dark-brown coloration in aqueous alcoholic $FeCl_3$ solution.

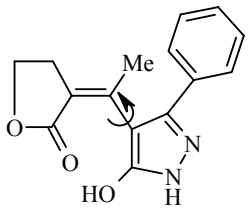
α-Acetylbutyrolactone reacted anomalously in its reaction with 3-phenyl- and 3-*p*-methoxyphenylpyrazol-5-ones. Condensation under standard conditions (170°C, 3 h) of α-acetylbutyrolactone with 3-phenylpyrazol-5-one and 3-*p*-methoxyphenylpyrazol-5-one gave compounds whose ^{1}H NMR spectra showed an anomalously large chemical shift for the triplet due to the OCH_2 (~4.15 ppm) whereas, in the alcohols with the expected structures **8** and **9**, the shift for the CH_2O group occurs at ~3.5 ppm.



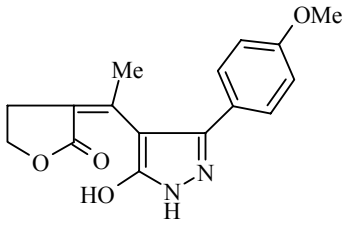
8–10

8 R = Ph; **9** R = *p*-$MeOC_6H_4$; **10** R = Me

In compound **10** the chemical shift occurs at 3.48 ppm (see Experimental). Upon acylation of the alcohol OH group this signal is shifted to low field by ~ 0.5-0.8 ppm which leads us to propose the alternative structures **8a** and **9a** for compounds **8** and **9**. This is supported by the presence in the ^{1}H NMR spectrum of low field signals at 10-12 ppm (NH and phenolic OH group protons) and the absence of a signal for the alcoholic OH group at 3-5 ppm (for compound **10** the signal for the OH group proton occurs at 4.4 ppm). In addition, compounds **8a** and **9a** gave positive reactions with $FeCl_3$ (the appearance of a dark-brown coloration).

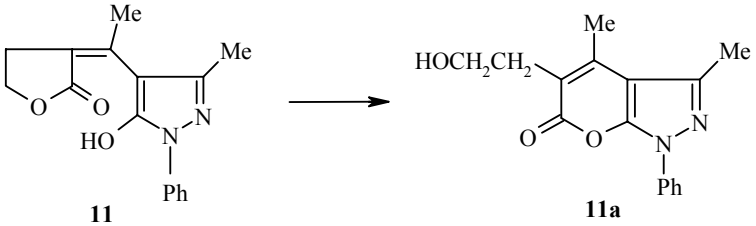


8a



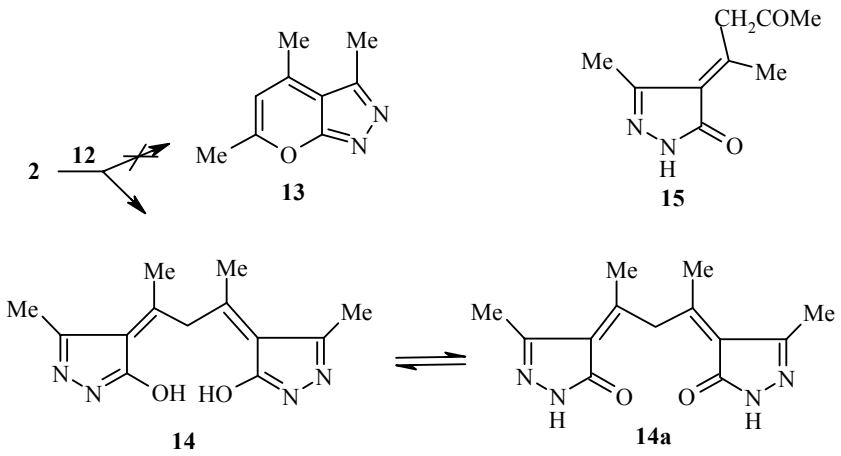
9a

However, the mass spectrum of **8a** shows a strong peak for $[M-31]^+$ (second in intensity after $[M]^+$) corresponding to $[M-CH_2OH]^+$, which is not typical of butyrolactones. In this connection we recorded the mass spectrum of the model compound **11** with known structure and also observed a strong peak for $[M-31]^+$. Further investigation has shown that compound **11** rearranges to compound **11a** upon heating to 180°C. This rearrangement, occurring in the ionization chamber under direct introduction conditions at high temperature (300°C), is the reason for the appearance of the $[M-31]^+$ ion.



11 **11a**

To clarify the conditions for the possible rearrangement of the pyrazololactone **8a** to the pyranopyrazole **8** we have found that the rearrangement occurs partially at 280°C. The ^{1}H NMR spectrum of the obtained reaction product showed both the signals for the starting **8a** (see Experimental) and those corresponding to structure **8** at 3.60 (t, OCH_2), 2.71 (t, CH_2), 2.11 (s, CH_3), and 7.50-7.38 ppm (m, H_{arom}). The reasons for the condensation halting at the first stage (**8a** and **9a**) are the steric hindrance due to the bulky substituent in position 3 of the pyrazolone ring which leads to rotation about the C–C axis and distancing of the OH group from the O–CO fragment making closure of the ring impossible.



Condensation of acetylacetone **12** with the pyrazolone **2** could have led to the pyranopyrazole **13** but heating pyrazolone **2** with an excess of **12** for 6 h led only to the product of condensation of two molecules of the pyrazolone with one molecule of acetylacetone to give compound **14**. It was of interest that the product of monocondensation was not produced despite the excess of acetylacetone. The condensation product **14a** (prepared previously in [3]) was insoluble in alkali but it did not have a C=O group absorption band in the region 1620-1800 cm^{-1} in the IR spectrum. This can be explained by its existence in the tautomeric form **14** and this is in good agreement with the ^{1}H NMR spectrum. The hydroxyl groups in compound **14** evidently do not possess sufficient acidity, hence its insolubility in alkali. However, the material gives a positive reaction with $FeCl_3$ (dark-brown coloration). The pyrazolone **2** does not react with dibenzoylmethane when heated at 160°C for 3 h and was recovered from the reaction unchanged.

EXPERIMENTAL

^{1}H NMR spectra were taken on a Bruker AM-300 instrument (300 MHz) using DMSO-d_6 and TMS as internal standard. UV spectra were recorded on a Specord M-40 instrument using alcohol and IR spectra on a Perkin-Elmer apparatus using KBr.

Synthesis of Pyrano[2,3-*c*]pyrazol-6-ones (General Method). The pyrazol-5-one (0.05 mol) and the corresponding β-keto ester (0.055 mol) were heated in a flask (50 ml) on a metal bath at 150-190°C for 2-4 h, distilling off the water and alcohol. After cooling the flask, ethyl acetate (20 ml) was added and the product was heated to reflux for 15 min. The reaction mixture was cooled and the precipitate was filtered and recrystallized from the corresponding solvent.

3,4-Dimethylpyrano[2,3-*c*]pyrazol-6-one (7a). Heated for 2 h at 145-155°C, yield 78%; mp 252°C (sealed capillary) (60% alcohol). IR spectrum, ν, cm^{-1}: 1520, 1610, 1700 (C=O). UV spectrum, λ_{max}, nm (log ε): 227 (3.31); 299 (4.26). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.47 (3H, s, CH_3-3); 2.36 (3H, d, *J* = 1.1, CH_3-4); 5.8 (1H, q, *J* = 1.1, H-5); 12.9 (1H, br. s, NH). Negative reaction with $FeCl_3$ (mp 245°C [4]).

3,4,5-Trimethylpyrano[2,3-*c*]pyrazol-6-one (7b). Heated for 3 h at 180°C, yield 65%; mp 257°C (sealed capillary) (ethyl acetate). IR spectrum, ν, cm^{-1}: 1540, 1610, 1710 (C=O). UV spectrum, λ_{max}, nm (log ε): 223 (3.65); 231 (3.65); 282 (4.38). ^1H NMR spectrum, δ, ppm: 1.98 (3H, s, CH_3-5); 2.34 (3H, s, CH_3-4); 2.49 (3H, s, CH_3-3); 12.7 (1H, br. s, NH). Found, %: C 60.3; H 5.8; N 15.9; $[M]^+$ 178. $C_9H_{10}N_2O_2$. Calculated, %: C 60.7; H 5.6; N 15.9; $[M]^+$ 178. Negative reaction with $FeCl_3$.

5-Ethyl-3,5-dimethylpyrano[2,3-*c*]pyrazol-6-one (7c). Heated for 3 h at 180°C, yield 42%; mp 206°C (ethyl acetate). IR spectrum, ν, cm^{-1}: 1535, 1610, 1715 (C=O). UV spectrum, λ_{max}, nm (log ε): 220 (3.49); 228 (3.44); 296 (4.11). ^1H NMR spectrum, δ, ppm: 1.03 (3H, t, CH_3-5); 2.32 (3H, s, CH_3-4); 2.49 (3H, s, CH_3-3); 2.52 (2H, q, CH_2-5); 12.7 (1H, br. s, NH). Found, %: C 62.1; H 6.3; N 15.1; $[M]^+$ 192. $C_{10}H_{12}N_2O_2$. Calculated, %: C 62.5; H 6.3; N 14.6; $[M]^+$ 192. Negative reaction with $FeCl_3$.

3,4-Dimethyl-5-propylpyrano[2,3-*c*]pyrazol-6-one (7d). Heated for 3 h at 180°C, yield 43%; mp 182°C (ethyl acetate). IR spectrum, ν, cm^{-1}: 1540, 1610, 1710 (C=O). UV spectrum, λ_{max}, nm (log ε): 231 (3.59); 303 (4.19). ^1H NMR spectrum, δ, ppm: 0.96 (3H, t, CH_3-5); 1.43 (2H, m, CH_2-5-β); 2.36 (3H, s, CH_3-4); 2.44 (2H, t, CH_2-5-α); 2.52 (3H, s, CH_3-3); 12.7 (1H, br. s, NH). Found, %: C 64.1; H 6.7; N 13.6. $C_{11}H_{14}N_2O_2$. Calculated, %: C 64.4; H 6.5; N 13.3. Negative reaction with $FeCl_3$.

5-β-Hydroxyethyl-3,4-dimethylpyrano[2,3-*c*]pyrazol-6-one (10). Heated for 3 h at 175°C, yield 60%; mp 282-284°C (sealed capillary) (ethanol). IR spectrum, ν, cm^{-1}: 1535, 1610, 1720 (C=O). UV spectrum, λ_{max}, nm (log ε): 227 (3.48); 266 (3.62); 303 (4.12). ^1H NMR spectrum, δ, ppm: 2.38 (3H, s, CH_3-3); 2.52 (3H, s, CH_3-4); 2.63 (2H, t, CH_2-5-α); 3.48 (2H, t, CH_2-O-5-β); 12.85 (1H, br. s, NH). Found, %: C 57.2; H 5.7; N 13.4. $C_{10}H_{12}N_2O_3$. Calculated, %: C 57.7; H 5.7; N 13.5. Negative reaction with $FeCl_3$.

3-Methyl-4-phenylpyrano[2,3-*c*]pyrazol-6-one (7e). Heated for 3 h at 155°C, yield 21%; mp 192-194°C (50% acetic acid). IR spectrum, ν, cm^{-1} 1510, 1595, 1670, 1730 (C=O). UV spectrum, λ_{max}, nm (log ε): 257 (3.81), 312 (4.04). ^1H NMR spectrum, δ, ppm: 2.09 (3H, s, CH_3-3); 5.86 (1H, s, H-5); 7.52 (5H, s, C_6H_5); 13.0 (1H, br. s, NH). Found, %: C 68.7; H 4.6; N 12.3. $C_{13}H_{10}N_2O_2$. Calculated %: C 69.0; H 4.4; N 12.4.

4-*p*-Methoxyphenyl-3-methylpyrano[2,3-*c*]pyrazol-6-one (7f). Heated for 3 h at 155°C, yield 17%; mp 195-197°C (70% acetic acid). IR spectrum, ν, cm^{-1}: 1510, 1585, 1685 (C=O). UV spectrum, λ_{max}, nm (log ε): 303 (4.24). ^1H NMR spectrum, δ, ppm: 2.14 (3H, s, CH_3-3); 3.84 (3H, s, O-CH_3); 5.81 (1H, s, H-5); 7.17 (2H, d, *o*-H_{arom}); 7.50 (2H, d, *m*-H_{arom}); 13.0 (1H, br. s, NH). Found, %: C 66.1; H 4.6; N 10.7. $C_{14}H_{12}N_2O_3$. Calculated, %: C 65.6; H 4.7; N 10.9. Negative reaction with $FeCl_3$.

5-Carbethoxymethyl-3,4-dimethylpyrano[2,3-*c*]pyrazol-6-one (7g). Heated for 2 h at 175°C, yield 29%; mp 170-172°C (ethyl acetate). IR spectrum, ν, cm^{-1}: 1580, 1610, 1695 (C=O). UV spectrum, λ_{max}, nm (log ε): 220 (3.65); 302 (4.19). ^1H NMR spectrum, δ, ppm: 1.20 (3H, t, $OCH_2C\underline{H}_3$); 2.44 (3H, s, CH_3-4); 2.55 (3H, s, CH_3-3); 3.52 (2H, s, CH_2-5); 4.10 (2H, q, $OC\underline{H}_2CH_3$); 12.8 (1H, br. s, NH). Found, %: C 57.3; H 5.6; N 11.3. $C_{12}H_{14}N_2O_4$. Calculated, %: C 57.6, H 5.6; N 11.3. Negative reaction with $FeCl_3$.

4-Methyl-3-phenylpyrano[2,3-*c*]pyrazol-6-one (7h). Heated for 3 h at 180°C, yield 69%; mp 194-195°C (ethanol). IR spectrum, ν, cm^{-1}: 1510, 1590, 1690 (C=O). UV spectrum, λ_{max}, nm (log ε): 250 (3.98); 302 (4.18). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.14 (3H, d, *J* = 1.1, CH_3-4); 5.83 (1H, q, *J* = 1.1, H-5); 7.35-7.42 (5H, m, H_{arom}). Found, %: C 69.1; H 4.4; N 12.1. $C_{13}H_{10}N_2O_2$. Calculated, %: C 69.0; H 4.4; N 12.0. Negative reaction with $FeCl_3$ (mp 190°C [4]).

3-*p*-Methoxyphenyl-4-methylpyrano[2,3-*c*]pyrazol-6-one (7i). Heated for 3 h at 160°C, yield 86%; mp 231-233°C (ethyl acetate). IR spectrum, ν, cm^{-1}: 1525, 1600, 1710 (C=O). UV spectrum, λ_{max}, nm (log ε): 229 (4.19); 250 (4.03); 307 (4.40). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.12 (3H, d, *J* = 1.1, CH_3-4); 3.84 (3H, s, OCH_3); 5.86 (1H, q, *J* = 1.1, H-5); 7.12 (2H, d, *m*-H_{arom}); 7.9 (2H, d, *J* = 6, *o*-H_{arom}); 11.8 (1H, very br. s, NH). Found, %: C 66.1; H 4.8; N 11.2. $C_{14}H_{12}N_2O_3$. Calculated, %: C 65.6; H 4.7; N 10.9. Negative reaction with $FeCl_3$.

4,5-Dihydro-3-[1-(5-hydroxy-3-phenyl-1H-pyrazol-4-yl)ethylidene]furan-2-one (8a). Heating for 3 h at 170°C, yield 69%; mp 282-284°C (ethyl acetate). IR spectrum, ν, cm^{-1}: 1515, 1630, 1710 (C=O). UV spectrum, λ_{max}, nm (log ε): 235 (4.48); 250 (4.42); 290 (4.33). ^1H NMR spectrum, δ, ppm: 2.29 (3H, s,

CH_3-4); 2.60 (2H, t, CH_2-5-α); 4.14 (2H, t, CH_2-5-β); 7.35-7.42 (5H, m, H_{arom}). Mass spectrum, *m/z* (I_{rel}, %): 270 $[M]^+$ (100); 255 (51); 239 $[M^+-CH_2OH]$ (88); 211 (74); 77 (68). Found, %: C 66.7; H 5.4; N 10.4. $C_{15}H_{14}O_3N_2$. Calculated, %: C 66.7; H 5.4; N 10.4. Negative reaction with $FeCl_3$.

4,5-Dihydro-3-{1-[5-hydroxy-3-(4-methoxyphenyl)-1H-pyrazol-4-yl]ethylidene}furanone (9a). Heating for 3 h at 170°C, yield 59%; mp 273-275°C (ethyl acetate). IR spectrum, ν, cm^{-1}: 1500, 1525, 1610, 1710 (C=O). UV spectrum, λ_{max}, nm (log ε): 251 (4.05); 286 (3.90). ^1H NMR spectrum, δ, ppm: 2.29 (3H, s, CH_3-4); 2.59 (2H, t, CH_2-5-α); 3.78 (3H, s, OCH_3); 4.13 (2H, t, CH_2-5-β); 6.98 (2H, d, *m*-H_{arom}); 7.37 (2H, d, *o*-H_{arom}). Found, %: C 64.0; H 5.3; N 9.4. $C_{16}H_{16}N_2O_4$. Calculated, %: C 64.0; H 5.3; N 9.3. Positive reaction with $FeCl_3$.

2,4-Bis(3-methyl-5-oxopyrazol-4-ylidene)pentanediylidene (14). A mixture of 3-methylpyrazol-5-one (2.94 g, 0.03 mol) and acetylacetone (4 g, 0.04 mol) was heated in a metal bath for 6 h at 140°C, distilling off the water. During the heating a further 2 g of acetylacetone was added portionwise. The reaction product was cooled and then heated to reflux with a mixture of benzene (10 ml) and hexane (4 ml). The precipitate was filtered off, washed with hexane, and then heated to reflux with acetone (10 ml) to purify it from colored admixtures. It was then filtered off and recrystallized from ethanol to give compound **14** (2.6 g, 67%); mp 232-234°C (sealed capillary). IR spectrum, ν, cm^{-1}: 1270, 1450, 1505, 1530, 1600, 2800-3180. ^1H NMR spectrum, δ, ppm: 1.79 (3H, s, CH_3-aliph.); 1.98 (2H, s, CH_2); 2.31 (3H, s, CH_3-pyrazole); 11.5 (1H, br. s, OH). Found, %: C 60.1; H 6.3; N 21.5. $C_{13}H_{16}N_4O_2$. Calculated, %: C 60.0; H 6.15; N 21.5. Positive reaction with $FeCl_3$ (mp 206°C [3]).

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