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The study of reactions of 7-substituted 8-hydrazino-3-methylxanthine with β-dicarbonyl compounds

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Key words: *Xanthine, Organic Synthesis, NMR-Spectroscopy, Mass Spectrometry.*

The problem of searching biologically active compounds amidst xanthine derivatives is a crucial one and is an issue for long-term investigation.

The aim of this paper was to study reactions of 7-substituted 8-hydrazino-3methylxanthine with acetylacetone and acetoacetic ether.

Methods and results. Reaction of 7-substituted 8-hydrazinoxanthines together with acetylacetone is performed by way of forming the respective 7-substituted 8-(3,4-dimethylpyrazole-1-yl)-3-methylxanthines.

Interaction of hydrazinoxanthines with the excess of acetoacetic ether proceeds with the formation of 8-(3,4-dimethyl-6-oxopyrano[2,3-s]pyrazol-1-yl)xanthines.

Conclusion. The investigated spectral characteristics of synthesized compounds indicate of relevance of IR-, NMR- and mass spectra to the proposed structure –(3,4-dimethyl-6-oxopyrano[2,3-s]pyrazol-1-yl)xanthines and 7-substituted 8-(3,4-dimethylpyrazole-1-yl)-3-methylxanthine.

Вивчення реакцій 7-заміщених 8-гідразино-3-метилксантину з β-дикарбонільними сполуками

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Проблема пошуку біологічно активних сполук серед похідних ксантину актуальна та перспективна. Мета роботи – вивчення реакцій 7-заміщених 8-гідразино-3-метилксантину з ацетилацетоном та ацетоацетатним естером. Реакція 7-заміщених 8-гідразино-3-метилксантину з ацетилацетоном реалізується утворенням відповідних 8-(3,4-диметилпіразол-1-іл)-3-метилксантинів. Взаємодія гідразиноксантинів із надлишком ацетоацетатного естера перебігає з утворенням 8-(3,4-диметил-6-оксопірано[2,3-с]піразол-1-іл)ксантинів. Досліджені спектральні характеристики синтезованих сполук свідчать про відповідність ІЧ-, ПМР- та мас-спектрів запропонованій будові 8-(3,4-диметил-6-оксопірано[2,3-с]піразол-1-іл)ксантинів і 7-заміщених 8-(3,4-диметилпіразол-1-іл)-3-метилксантину.

Ключові слова: *ксантин, органічний синтез, ПМР-спектроскопія, мас-спектрометрія.*

Актуальні питання фармацевтичної і медичної науки та практики. – 2015. – № 2 (18). – С. 4–8

Изучение реакций 7-замещенных 8-гидразино-3-метилксантина с β-дикарбонильными соединениями

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Проблема поиска биологически активных соединений среди производных ксантина актуальна и перспективна. Целью работы являлось изучение реакций 7-замещенных 8-гидразино-3-метилксантина с ацетилацетоном и ацетоуксусным эфиром. Реакция 7-замещенных 8-гидразиноксантинов с ацетилацетоном реализуется образованием соответствующих 8-(3,4-диметилпиразол-1-ил)-3-метилксантинов. Взаимодействие гидразиноксантинов с избытком ацетоуксусного эфира протекает с образованием 8-(3,4-диметил-6-оксопирано[2,3-с]пиразол-1-ил)ксантинов. Исследованные спектральные характеристики синтезированных соединений свидетельствует о соответствии ИК-, ПМР- и масс-спектров предложенной структуре 8-(3,4-диметил-6-оксопирано[2,3-с]пиразол-1-ил)ксантинов и 7-замещенных 8-(3,4-диметилпиразол-1-ил)-3-метилксантина.

Ключевые слова: *ксантин, органический синтез, ПМР-спектроскопия, масс-спектрометрия.*

Актуальные вопросы фармацевтической и медицинской науки и практики. – 2015. – № 2 (18). – С. 4–8

Continuing studies of chemical and biological properties of 7,8-disubstituted 3-methylxanthine [1–8], we investigated the reaction of 7-substituted 8-hydrazino-3-methylxanthine with acetylacetone and acetoacetic ester to obtain 8-(1-pyrazolyl-1-)xanthines, which have not been studied previously in any chemical nor biological aspect.

The aim of the research was to study the reactions of 7-substituted-8-hydrazino-3-methylxanthine with acetylacetone and acetoacetic ester.

Materials and methods

The melting point has been determined by open capillary method on the device PTP (M). Elemental analysis has been performed on the device Elementar Vario L cube. NMR spectra have been taken using spectrometer Bruker SF-200 (operating frequency was 200 MHz and the solvent was DMSO, internal standard was TMS). Mass spectra have been recorded with the device «Varian 1200L», ionization - electron impact (70eV) by direct introduction of the sample. IR spectra have been taken using the Bruker Alpha device in the 4000-400 cm^{-1} using the ATR prefix (direct introduction of the substance). These physical-chemical properties of the synthesized compounds are shown in *Table 1* and *2*.

The synthesis of 8-bromo-7-ethyl**(1)**-, propyl**(2)**-3-methylxanthines is described in the work [1]. Synthesis of 8-bromo-7-*i*-butyl-3-methylxanthine **(3)**, 7-*i*-amyl-8-bromo-3-methylxanthine **(4)**, 8-bromo-3-methyl-7-(2-methoxyethyl) xanthine derivatives **(6)**, 8-bromo-3-methyl-7-(2-phenoxyethyl) xanthine **(7)** is described in works [2-5], respectively.

Table 1

^{1}H NMR spectra of synthesized compounds

Substance	The chemical shifts of protons, δ- scale, ppm							
	N^1H (s, 1H)	CH ar.	$CH_{pyraz.,\ pyran.}$ (s, 1H)	N^7CH_2 (2H)	N^3CH_3 (s, 3H)	$C_{3',4'}$-CH_3 (s, 3H)	$C_{3,5}$-CH_3 pyraz. (s, 3H)	Other
5	10.72	–	–	4.62 (d)	3.32	–	–	5.18 (t, 1H) – C=CH; 1.68 (s, 3H) – CH_3; 1.61 (s, 3H) – CH_3
8	10.50	7.09 (q, 4H)	–	5.28 (s)	3.28	–	–	2.32 (s, 3H) – Ar-CH_3
9	11.19	7.52 (d, 2H); 7.33 (t, 1H); 7.22 (d, 1H)	–	5.49 (s)	3.33	–	–	–
13	10.61	–	–	3.99 (t)	3.29	–	–	8.10 (s, 1H) – NH; 4.38 (bs, 2H) – NH_2; 1.48 (m, 3H) – CH_2CH; 0.87 (d, 6H) – $CH(CH_3)_2$
14	10.63	–	–	4.62 (d)	3.29	–	–	8.09 (s, 1H) – NH; 4.36 (bs, 2H) – NH_2; 5.16 (tt, 1H) – CH; 1.69 (s, 3H) – CH_3; 1.61 (s, 3H) – CH_3
15	10.63	–	–	4.15 (t)	3.30	–	–	8.0 (s, 1H) – NH; 4.35 (bs, 2H) – NH_2; 3.51 (t, 2H) – OCH_2; 3.19 (s, 3H) – OCH_3
16	10.43	7.23 (t, 2H); 6.87 (m, 3H)	–	4.42 (t)	3.35	–	–	8.03 (s, 1H) – NH; 4.12 (bs, 2H) – NH_2; 4.20 (t, 2H) – OCH_2
17	10.38	7.31 (q, 4H)	–	5.31 (s)	3.32	–	–	8.14 (s, 1H) – NH; 4.25 (bs, 2H) – NH_2; 2.22 (s, 3H) – $ArCH_3$
18	10.42	7.50 (d, 2H); 7.29 (t, 1H); 7.18 (d, 1H)	–	5.50 (s)	3.32	–	–	8.10 (s, 1H) – NH; 4.28 (bs, 2H) – NH_2
19	11.28	–	6.17	4.20 (q)	3.30	–	2.31; 2.18	1.55 (t, 3H) – CH_3
20	11.27	–	6.19	4.21 (t)	3.32	–	2.30; 2.20	1.62 (m, 2H) – CH_2; 0.68 (t, 3H) – CH_3
21	11.30	–	6.16	4.45 (t)	3.35	–	2.28; 2.18	3.49 (t, 2H) – OCH_2; 2.98 (s, 3H) – OCH_3
22	11.09	7.15 (t, 2H); 6.83 (t, 1H); 6.69 (d, 2H)	6.02	4.87 (t)	3.41	–	2.40; 2.23	4.24 (t, 2H) – OCH_2
23	11.35	–	6.0	4.21 (q)	3.31	2.49-2.45	–	1.31 (t, 3H) – CH_3
24	11.38	–	6.01	4.20 (t)	3.31	2.49-2.45	–	1.70 (m, 2H) – CH_2; 0.71 (t, 3H) – CH_3
25	11.38	–	6.02	4.12 (d)	3.31	2.49-2.45	–	2.0 (m, 1H) – CH; 0.70 (d, 6H) – $CH(\underline{CH_3})_2$
26	11.34	–	6.02	4.21 (t)	3.31	2.49-2.44	–	1.64 (q, 2H) – CH_2; 1.44 (m, 1H) – CH; 0.77(d, 6H) – $CH(\underline{CH_3})_2$
27	11.35	–	6.0	4.49 (d)	3.33	2.49-2.44	–	5.12 (t, 1H) – C=CH; 1.53 (s, 3H) – CH_3; 1.46 (s, 3H) – CH_3
28	11.39	–	6.0	4.41 (t)	3.32	2.5	–	3.49 (t, 2H) – OCH_2; 2.94 (s, 3H) – OCH_3
29	11.42	7.09 (t, 2H); 6.80 (t, 1H); 6.57 (d, 2H)	5.99	4.78 (t)	3.34	2.35 (d. 6H)	–	4.25 (t, 2H) – OCH_2
30	11.42	6.99 (d, 2H); 6.88 (d, 2H)	5.97	5.49 (s)	3.33	2.50; 2.42	–	2.12 (s, 3H) – $ArCH_3$
31	11.43	7.39 (d, 1H); 7.30-7.05 (m, 3H)	5.98	5.50 (s)	3.31	2.50-2.45	–	–

The synthesis of 8-bromo-3-methyl-7-(3-methylbutene-2-yl-1)xanthine **(5)**. The mixture of 36.7 g (0.15 mol) of 8-bromo-3-methylxanthine [1], 16.9 ml (0.15 mol) of 3-methyl-1-chlorobutene-2, 12.6 g (0.15 mol) of $NaHCO_3$ and 200 ml of DMF was boiled for 1 hour and filtered. The filtrate was cooled, 200 ml of water was added, the residue was filtered off, washed first with a 5% solution of NH_4OH, then washed with water and crystallized from aqueous dioxane.

7-benzyl substituted **8** and **9** have been prepared similarly (in aqueous dioxane).

Hydrazinoxanthines **10-12** have been obtained by the method [2].

The synthesis of 7-*i*-amyl-8-hydrazino-3-methylxanthine **(13)**. The solution of 5.4 g (0.017 mol) bromoxanthine **4**, 10 ml (0.2 mol) of hydrazine hydrate in a mixture of 30 ml of water and 40 ml of dioxane was boiled for 2 hours, cooled, diluted with water to 150 ml and the precipitate was filtered off, washed with water and crystallized from aqueous dioxane.

Table 2

Physical-chemical properties of the synthesized compounds

Substance	Empirical formula	T. melt., °C	Yield, %	Substance	Empirical formula	T. melt., °C	Substance
5	$C_{11}H_{13}BrN_4O_2$	232–234	87	21	$C_{14}H_{18}N_6O_3$	150–151	40
8	$C_{14}H_{13}BrN_4O_2$	270–272	97	22	$C_{19}H_{20}N_6O_3$	157–158	90
9	$C_{13}H_{10}Br_2N_4O_2$	253–255	90	23	$C_{16}H_{16}N_6O_4$	295–296	28
13	$C_{11}H_{18}N_6O_2$	227–228	75	24	$C_{17}H_{18}N_6O_4$	265–266	22
14	$C_{11}H_{16}N_6O_2$	246–247	71	25	$C_{18}H_{20}N_6O_4$	236–237	25
15	$C_9H_{14}N_6O_3$	245–247	89	26	$C_{19}H_{22}N_6O_4$	256–257	35
16	$C_{14}H_{16}N_6O_3$	210–212	81	27	$C_{19}H_{20}N_6O_4$	255–256	43
17	$C_{14}H_{16}N_6O_2$	236–238	97	28	$C_{17}H_{18}N_6O_5$	259–260	27
18	$C_{13}H_{13}BrN_6O_2$	260–261	89	29	$C_{22}H_{20}N_6O_5$	224–225	38
19	$C_{13}H_{16}N_6O_2$	153–154	35	30	$C_{22}H_{20}N_6O_4$	253–254	30
20	$C_{14}H_{18}N_6O_2$	155–156	66	31	$C_{21}H_{17}BrN_6O_4$	207–208	48

Hydrazinoxanthines **14-18** have been obtained by the method [2].

The synthesis of 8-(3,5-dimethylpyrazole-1-yl)-3-methyl-7-etylxanthine **(19)**. The solution of 2.2 g (0.01 mol) hydrazinoxanthine **10**, 5 ml (0.05 mol) of acetylacetone in 10 ml of glacial CH_3COOH was boiled for 6 hours, cooled, water wax added to 50 ml. The residue was filtered off, washed with water and crystallized from aqueous dioxane.

Pyrazolylxanthines **20, 22** (from aqueous dioxane), **21** (from water) have been prepared similarly.

Mass spectrum of 8-(3,5-dimethylpyrazole-1-yl)-3-methyl-7-(2- methoxyethyl) xanthine **(21)** (EI, 70 eV), *m/z* (I_{rel}%): 318 $[M]^+$ (31.8); 286 (5.9); 260 (24.1); 134 (17.7); 109 (9.6); 108 (16.2); 107 (16.4); 106 (9.1); 70 (7.8); 45 (63.1); 44 (5.3); 43 (99.9); 42 (25.0); 41 (7.8).

The synthesis of 8-(3,4-dimethyl-6-oxopyrano[2,3-c] pyrazole-1-yl)-3-methyl-7-ethylxantine **(23)**. The solution of 2.2 g (0.01 mol) hydrazinoxanthine **10**, 6.4 ml (0.05 mol) of ethyl acetoacetate in 10 ml of glacial CH_3COOH was boiled for 6 hours, cooled, 50 ml of 30% 2-propanol was added and left at room temperature for 1 day. The residue was filtered off, washed with water and crystallized from aqueous DMF.

Pyranopyrazoles **24-31** have been prepared similarly. Compounds **24, 26, 27, 29-31,** recrystallized from aqueous dioxane, **25, 28** - from aqueous 2-propanol.

Mass spectrum of 8-(3,4-dimethyl-6-oxopyrano[2,3-c] pyrazole-1-yl)-3-methyl-7-ethylxantine (**23**) (EI, 70 eV), *m/z* (I_{rel}, %): 356 $[M]^+$ (27.1); 330 (5.3); 136 (5.4); 135 (9.7); 134 (5.6); 125 (6.7); 123 (6.7); 122 (6.7); 109 (9.9); 108 (17.0); 107 (21.7); 97 (9.8); 96 (8.1); 95 (17.6); 94 (19.5); 93 (11.4); 83 (5.1); 82 (32.5); 81 (16.5); 80 (25.4); 79 (16.3); 78 (17.0); 77 (33.8); 70 (29.9); 69 (10.2); 68 (25.9); 67 (99.9); 66 (9.5); 65 (9.1); 61 (7.0); 53 (16.0); 52 (27.9); 51 (14.2).

Mass spectrum of 8-(3,4- dimethyl -6- oxopyrano [2,3-c] pyrazole-1-yl)-3- methyl-7-*н*-propylxantine (**24**) (EI, 70 eV), *m/z* (I_{rel}, %): 371 $[M]^+$+1 (22.3); 370 $[M]^+$ (99.6); 355 (6.2); 345 (6.0); 344 (14.3); 341 (12.1); 329 (17.6); 328 (99.9); 327 (6.9); 150 (6.5); 149 (5.8); 135 (5.4); 121 (5.3); 109 (7.3); 108 (10.5); 107 (10.8); 94 (6.4); 93 (6.7); 82 (19.6); 81 (12.3); 80 (15.9); 79 (9.6); 78 (9.9); 77 (19.6); 70 (5.4); 68 (12.8); 67 (24.1); 53 (11.3); 52 (17.7); 51 (7.1).

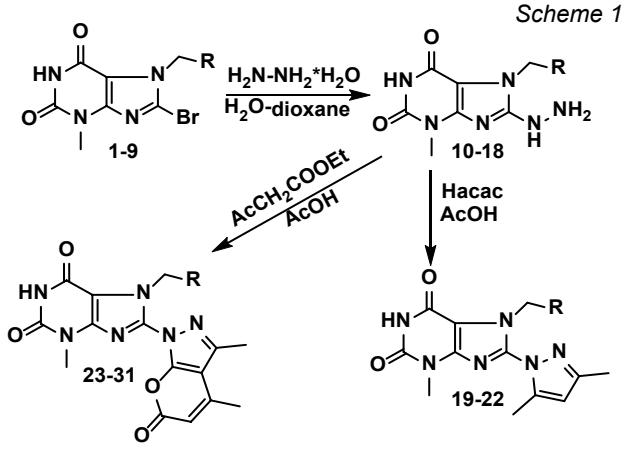
Mass spectrum of 8-(3,4-dimethyl-6-oxopyrano[2,3-c] pyrazole-1-yl)-3-methyl-7-(2-methoxyethyl)xantine (**28**) (EI, 70 eV), *m/z* (I_{rel}, %): 387 $[M]^+$+1 (8.2); 386 $[M]^+$ (47.2); 329 (15.4); 328 (83.1); 165 (5.7); 150 (12.1); 149 (12.5); 147 (5.3); 136 (7.0); 135 (15.3); 134 (19.2); 123 (8.1); 122 (15.3); 121 (21.7); 120 (13.8); 111 (5.6); 109 (21.9); 108 (44.6); 107 (53.1); 106 (14.4); 96 (6.4); 95 (15.8); 94 (30.7); 93 (35.5); 92 (14.8); 84 (9.5); 83 (13.1); 82 (52.9); 81 (52.4); 80 (58.1); 79 (37.5); 78 (49.6); 77 (84.2); 70 (31.1); 69 (13.9); 68 (16.3); 67 (73.9); 66 (16.3); 65 (12.9); 63 (6.0); 61 (10.1); 60 (8.0); 59 (99.9); 58 (60.4); 56 (6.7); 55 (11.3); 54 (19.8); 53 (43.6); 52 (84.2); 51 (29.7); 50 (10.0).

Mass spectrum of 8-(3,4-dimethyl-6-oxopyrano[2,3-c] pyrazole-1-yl)-3-methyl-7-(4-methylbenzyl)xantine (**30**) (EI, 70 eV), *m/z* (I_{rel}, %): 432 $[M]^+$ (11.0); 328 (5.3); 135 (6.1); 106 (15.0); 105 (99.9); 104 (6.1); 103 (7.7); 79 (8.5); 77 (11.0).

Results and Discussion

The starting 7-substituted 8-bromo-3-methylxanthine **(1-4, 6,7)** have been described previously [1-5]. The synthesis of bromoxantines **5, 8, 9** has been performed by briefly boiling of 8-bromo-3-methylxanthine [1] with the corresponding halogen derivatives in DMF with the presence of equimolar amounts of $NaHCO_3$. Number of 7-substituted-8-hydrazino-3-methylxanthine **(10-18)** has been obtained by the reaction of bromoxantines **1-9** with excess of hydrazine hydrate in aqueous dioxane (*Scheme 1*).

Scheme 1



1, 10, 19, 23 (R=CH_3); 2, 11, 20, 24 (R=C_2H_5); 3, 12, 25 (R=$CH(CH_3)_2$); 4, 13, 26 (R=$CH_2CH(CH_3)_2$); 5, 14, 27 (R=$CH{=}C(CH_3)_2$); 6, 15, 21, 28 (R=CH_2OCH_3); 7, 16, 22, 29 (R=$CH_2OC_6H_5$); 8, 17, 30 (R=$C_6H_4CH_3$-p); 9, 18, 31 (R=C_6H_4Br-m)

As it is shown in Scheme 1, the reaction of hydrazinoxantines **10, 11, 15, 16** with acetylacetone in glacial acetic acid is implemented to form the corresponding 7-substituted-8-(3,4-dimethylpyrazole-1-yl)-3-methylxanthines **(19-22)** which is typical for other heterylhydrazines [9, 10]. Presence of 3,5-dimethylpyrazole cycle at position 8 in xanthine molecule has been conclusively confirmed by PMR spectroscopy (*Table. 1*).

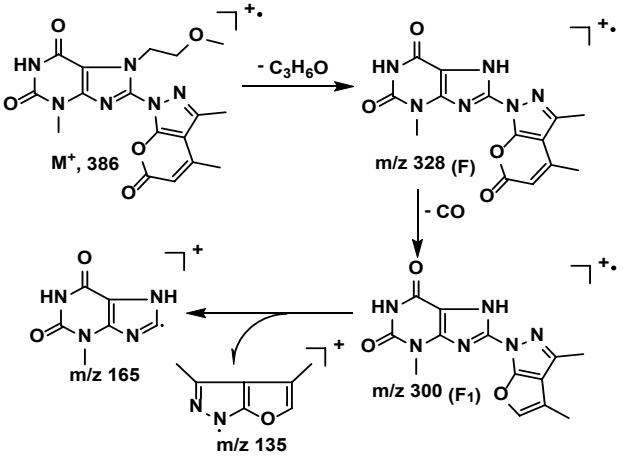
In the pyrazolylxantines **19-22** spectra, there is no signals of hydrazino protons, but two intensive singlets in 2.40-2.18 ppm are clearly fixed due to resonance absorption of the protons of the methyl group of the pyrazole nucleus. Aromatic protones at position 4 of pyrazole substituent were recorded as singlets with one proton intensity unit at 6.19-6.02 ppm. The protons signals of the uracil part of molecules and substituents in the 7-position fully consists with their structure.

The peak of the molecular ion with *m/z* 318 has been registered in the mass spectrum of 8-(3,5-dimethylpyrazole-1-yl)-3-methyl-7- (2-methoxyethyl) xanthine **(21)**, this peak corresponds to the calculated molecular weight and shows even number of nitrogen atoms in the molecule. Initial degradation processes of molecular ion are associated with partial and complete elimination of methoxyethyl substituent in position 7 of the molecule (F ion *m/z* 260) and subsequent decay of the uracil moiety. Ion *m/z* 43 (99.9%) is maximum in the spectrum and corresponds HNCO particle from the F ion.

Interaction of hydrazinoxantines **10-18** with the excess of acetoacetic ester in glacial acetic acid takes place with the formation of new derivatives of heterocyclic system, namely 8-(3,4-dimethyl-6-oxopyrano[2,3-c]pyrazole-1yl) xanthines **(23-31)** (Scheme 1) analogously to [11, 12]. The IR spectra of **23-31** pyranopyrazoles contain stretching vibrations band of carbonyl group of α-pyran nucleus, which is fixed at 1780-1744 cm^{-1}. For the PMR spectra of pyranopyrazoles **23-31** (*Table. 1*) the intense proton singlets of methyl groups are registered in the DMSO at 2.5-2.44 ppm and only for phenoxyethyl substituted **29** the doublet protons of two methyl groups with six proton intensity units at 2.35 ppm is registered. Proton signals at 5-position of the pyran ring is clearly captured in a relatively narrow range at 6.02-5.97 ppm (1H).

The protons' signals of other xanthine moiety deputies of pyranopyrazole substituted fully confirm their structure. Mass spectra of pyranopyrazoles **23, 24, 28, 30** contain molecular ion peaks, which are precisely fixed corresponding to calculated molecular masses. The possible decay of the initial nature of the 8-(3,4-dimethyl-6-oxopyrano[2,3-c] pyrazole-1-yl)-3-methyl-7-(2-methoxyethyl)xantine **(28)** molecular ion is shown in *Scheme 2*.

Scheme 2



As it is shown in Scheme 2, the initial fragmentation act M^+ of pyranopyrazole **28** is methyl vinyl ether- radical cleavage from position 7 and the formation of ions with *m/z* 328 (F), *m/z* 58 and *m/z* 59 (99.9%), besides the last one is the maximum one in the spectrum and corresponds to the structure of the protonated form of methyl vinyl ether. Later CO particle is cleaved from F ion and forms F_1 ion with *m/z* 300, which corresponds to the stable structure of furanopyrazole radical. Disintegration of F_1 ion leads to two ions with *m/z* 165 and *m/z* 135, confirming the presence of both xanthine and pyranopyrazole parts in molecule.

Thus, the above mentioned infoprmation confirms the astructure of the synthesized pyranopyrazoles **28-31**. In our opinion, the reaction of 8-hydraazynoxantines with excess of ethyl acetoacetate is common for mono-substituted of hydrazine, thus it will be necessary to investigate its mechanism and stereochemical features of pyranopyrazoles. One can assume that classical circuit of pyrazole nucleus occurs at the beginning, and then a second molecule of acetoacetic ester acts as an acylating and electrophilic reagent, which leads to the closure of the pyran ring.

Results

1. As a result of studies new derivatives of 8-(3,4-dimethyl-6-oxopyrano[2,3-c]pyrazol-1-yl)xanthine heterocyclic system have been obtained. A number of undocumented in the literature 7-substituted 8-(3,4-dimethylpyrazole-1-yl)-3-methylxanthines have been also received.

2. The structure of the synthesized compounds has been confirmed by IR and PMR spectroscopy and mass spectrometry.

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