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REACTION OF 3,5-CARBONYL-SUBSTITUTED 1,4-DIHYDROPYRIDINES WITH HYDRAZINE HYDRATE

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The interaction of 3,5-carbonyl-substituted derivatives of 1,4-dihydropyridine and some analogs of it with hydrazine hydrate occurs with fission of the heterocycle. In the case of alkoxycarbonyl-substituted compounds a reverse Michael reaction predominates leading to fragmentation of the molecules.

Keywords: 3-acyl- and 3-alkoxycarbonyl-5-oxo-1,4-dihydroindeno[1,2-*b*]pyridines, 3,5-acyl- and 3,5-alkoxycarbonyl-1,4-dihydropyridines, pyrazole derivatives, fission of heterocycle with hydrazine.

The majority of the known derivatives of 1,4-dihydropyridine have electron-withdrawing substituents, which usually contain a carbonyl group, in positions 3 and 5. Conjugation of the carbonyl substituents with the NH group of the 1,4-dihydropyridine ring reduces the tendency of these compounds towards oxidation, and simultaneously reduces the carbonyl reactivity and imparts weakly acidic properties to the ring NH group [1]. Consequently there is little information on the reactions of these compounds with hydrazines. For example, the preparation of the 2,4-dinitrophenylhydrazone of 3,5-diacetyl-1,4-dihydropyridine is known [2], as is the reaction of hydrazine with 2,3,5,6-tetraethoxycarbonyl-1,4-dihydropyridine, where the initial addition of hydrazine to the substituents in positions 2 and 6 facilitates intramolecular cyclization with the substituents in positions 3 and 5 [3]. This principle is also used in other syntheses of condensed heterocycles [4, 5]. The report on the preparation of the dihydrazide of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid [6] proved to be erroneous. It was later established that bis(5-methyl-3-oxo-4-pyrazolyl)methane is formed [7]. In the reactions of 3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine [7] and its 4-methyl, 4-ethyl, 4-phenyl, and 4-(2-chlorophenyl) derivatives, and also of 3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridine and its 4-methyl and 4-phenyl derivatives [8], with a small excess of hydrazine hydrate without solvent, decomposition of the heterocycle was observed and derivatives of bispyrazolylmethane were obtained. A large proportion of the reactions required extended (up to 65 h) heating.

We have studied this reaction with a wider circle of related compounds, with tricyclic and pentacyclic compounds containing the 1,4-dihydropyridine ring, and also with a tetrahydropyrimidine derivative. With the aim of accelerating the process we carried out the reaction of the compounds being studied with an excess of hydrazine hydrate in an autoclave at 100-150°C and in a solvent in order to avoid heterogeneous reactions.

Under these conditions the reaction of 3,5-acyl derivatives of 1,4-dihydropyridine **1a-f** with hydrazine hydrate proceeds more readily and pure bispyrazolylmethanes **2a-f** are formed in high yield. Compound **2b** [8] was obtained previously on cyclization of methylene-3,3'-bisacetylacetone with hydrazine.

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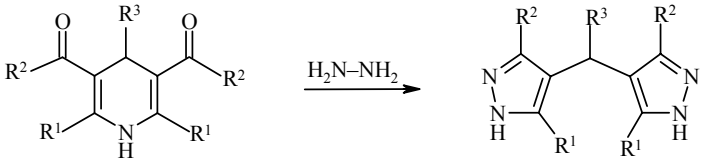
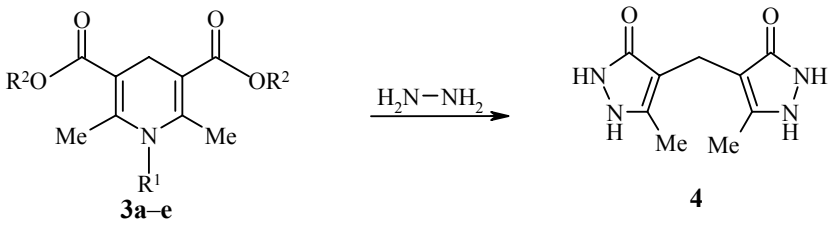


1a–f **2a–f**

1, **2 a** R^1 = H, R^2 = Me, R^3 = H; **b** $R^1 = R^2$ = Me; R^3 = H; **c** $R^1 = R^2$ = Me, R^3 = 3-Py; **d** $R^1 = R^2$ = Me, R^3 = 2-$C_6H_4OCHF_2$; **e** $R^1 = R^2$ = Me, R^3 = 3,4,5-$(MeO)_3C_6H_2$; **f** R^1 = Me, R^2 = Ph, R^3 = H

The reaction occurs even with compounds **1d** and **1e**, which have bulky substituents in position 4, and also with the 3,5-dibenzoyl-substituted 1,4-dihydropyridine **1f**. In difference to the data of [8] the solvent (ethanol) does not change the process.

Esters of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid **3a-d** react with hydrazine hydrate readily and unambiguously. The conversion of compound **3b** was also successful on boiling in ethanolic solution.

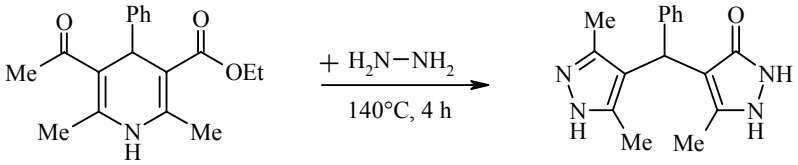


3a–e **4**

3 a R^1 = H, R^2 = Me; **b** R^1 = H, R^2 = Et; **c** R^1 = H, R^2 = menthyl; **d** R^1 = H, R^2 = $(CH_2)_{13}Me$; **e** R^1 = Me; R^2 = Et

Compound **4** was previously obtained on cyclization of methylene-2,2'-bisacetoacetic ester with hydrazine. The size of the ester radical R^2 has comparatively little influence on the reaction rate. Reaction with the N-methyl-substituted compound **3e** occurs more slowly. The formation of the second pyrazole ring requires elimination of methylamine.

The reaction may be used for obtaining unsymmetrical bispyrazolylmethanes. Compound **6** is formed from 3-acetyl-5-ethoxycarbonyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine (**5**) by reaction with hydrazine hydrate.

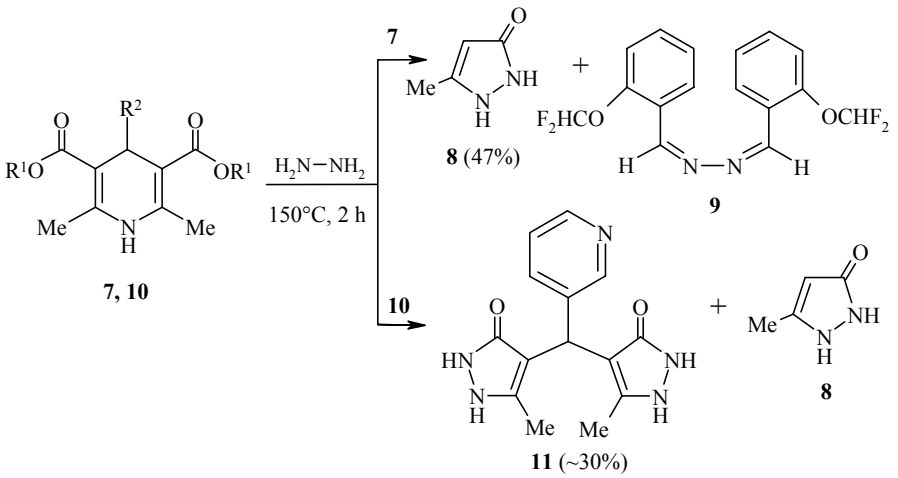


5 **6**

The structure of compound **6** was confirmed by the ^{1}H NMR spectrum, but the IR spectrum is similar to the spectra of bispyrazolylmethanes **2** and methylenebispyrazolone **4**. In the IR spectrum of the latter the stretching vibrations of the associated NH groups are displayed as bands in the 2400-3200 cm^{-1} region due to strengthening of the hydrogen bonds caused by resonance effects (of possible tautomeric bipolar structures). The presence of NH and C=O (or C–OH) groups are thereby masked [9].

The reaction of hydrazine hydrate with compounds **1b** and **3a-d** unsubstituted at position 4 proceeds significantly more rapidly than with their analogs substituted at position 4. This probably indicates the addition of hydrazine to the carbonyl group as the first stage of the process with subsequent intramolecular addition of the NH group at the $C_{(5)}$=$C_{(6)}$ double bond, with fission of the 1,4-dihydropyridine ring and the formation of a pyrazole.

4-Aryl-3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridines react poorly with hydrazine hydrate [8]. We carried out these reactions with an excess of hydrazine hydrate in alcohol solution at 130-150°C. In the case of the bulky 5-norbornen-2-yl substituent at position 4 the initial dihydropyridine remains unchanged. The 1,4-dihydropyridine ring is retained also in the case of the 4-phenyl-substituted compound, but its 4-(3-pyridyl) analog **10** reacted with ring fission and the formation of bispyrazolylmethane **11**. Reactions occurred readily with methyl esters but frequently in addition to the expected bispyrazolonylmethane derivative such products as 5-methyl-3-pyrazolone (**8**), and the hydrazone or azine of the aldehyde used for the synthesis of the corresponding dihydropyridine were formed. Consequently, the so-called reverse Michael reaction is observed.



7 R^1 = Me, R^2 = 2-$C_6H_4OCHF_2$; **10** R^1 = Et, R^2 = 3-Py

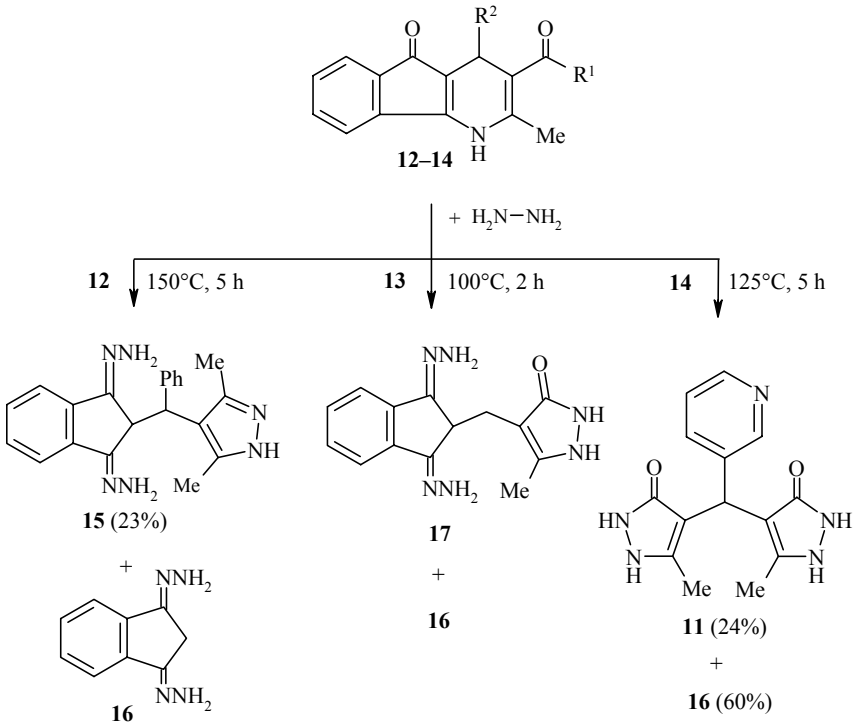
The yield of these side products in the reaction with dihydropyridine **7** exceeds the yield of the expected bispyrazolonylmethane.

The 1,4-dihydropyridine ring is also broken on treatment of derivatives of 1,4-dihydroindeno[1,2-*b*]-pyridine with hydrazine hydrate. It was possible to isolate compound **15** in the reaction with the 3-acetyl-substituted compound **12**. The reverse Michael reaction predominates in the reactions with the 3-alkoxycarbonyl derivatives **13** and **14** under these conditions. It was possible to isolate 1,3-indanedione dihydrazone (**16**) in up to 60% yield from the reaction mixture, and products of the recombination of fragments of the molecule, such as 3-pyridylbis(5-methyl-3-oxo-4-pyrazolyl)methane (**11**). Compound **13**, unsubstituted at position 4, forms a mixture of compounds even under less rigid conditions (Scheme 1).

In the case of 10,12-dioxo-11-phenyl-5,10,11,12-tetrahydrodiindeno[1,2-*b*:2',1'-*e*]pyridine (**18**), a polycyclic derivative of 1,4-dihydropyridine, heating with hydrazine hydrate takes place without fission of the heterocycle (Scheme 2).

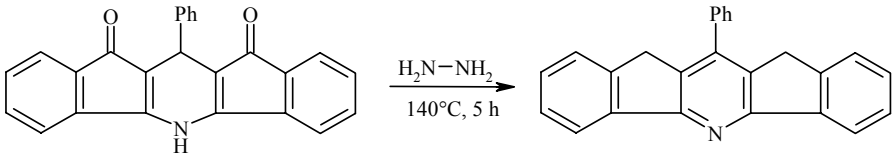
Under the reaction conditions probably addition of hydrazine to a carbonyl group occurs, which is accompanied by spontaneous aromatization of the heterocycle. Simultaneously a Wolff–Kishner reaction occurs and 11-phenyl-10H,12H-diindeno[1,2-*b*:2',1'-*e*]pyridine (**19**) is formed. Compound **19** was obtained previously from the product of oxidation of compound **18** [10].

Scheme 1



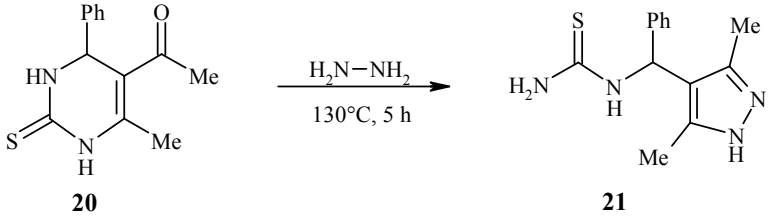
12 R^1 = Me, R^2 = Ph; **13** R^1 = OEt, R^2 = H; **14** R^1= OEt, R^2 = 3-Py

Scheme 2



18 **19**

Fission of the heterocycle and the formation of a pyrazole derivative also occurs on treatment of other related system with hydrazine hydrate.



20 **21**

3,5-Dimethyl-4-(α-thioureidobenzyl)pyrazole (**21**) is formed on interacting 5-acetyl-6-methyl-2-thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidine (**20**) with hydrazine hydrate.

TABLE 1. Reactions with Hydrazine Hydrate

Compound investigated			Hydrazine hydrate		Ethanol, ml	Reaction conditions		Product obtained		
No.	g	mmol	ml	mmol		t, °C	time, h	No.	amount, g	yield, %
1a	0.10	0.55	0.5	10.3	2.5	140	6	**2a**	0.05	52
1b	0.33	1.71	1.2	24.7	2.5	140	2	**2b**	0.28	80
1c	10.0	37.0	25	510	55	150	5	**2c**	7.69	74
1d	15.0	45.0	15	306	60	150	3	**2d**	14.10	91
1e	0.33	0.92	1.2	24.7	2.5	140	4	**2e**	0.20	59
1f	10.0	31.5	20	410	60	140	6	**2f**	8.80	85
3a	0.33	1.47	1.2	24.7	2.5	140	0.5	**4**	0.25	82
3b	30	120	60	1240	200	~80	6	**4**	21.73	88*
3c	0.33	0.70	1.2	24.7	2.5	140	1	**4**	0.12	83
3d	0.66	1.12	0.52	10.4	2.2	140	1	**4**	0.19	82
3e	0.34	1.27	1.2	24.7	2.5	140	6	**4**	0.12	45
5	0.33	1.10	1.2	24.7	2.5	140	4	**6**	0.23	74
7	10.0	27.2	20	410	60	150	5	**8**	2.50	47
10	10.0	30.3	20	410	60	150	5	**11**	0.91	11*[2]
12	0.33	1.05	1.2	24.7	2.5	140	6	**15**	0.10	27*[3]
13	0.33	1.23	1.2	24.7	2.5	100	2	**16+17**	Not isolated	
14	10.0	30.1	10	204	60	125	5	**16**	3.16	60
								11	1.04	24
18	0.06	0.17	0.5	10.3	2.5	140	5	**19**	0.02	36
20	10.0	40.6	25	510	55	130	5	**21**	9.90	37

* Boiling in a flask under reflux.

*[2] A mixture (2.28 g) of compounds **11** and **8** was isolated in addition.

*[3] A mixture (0.23 g) of compounds **15** and **16** was obtained on evaporation.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker WH-90 (90 MHz) spectrometer in DMSO-d_6, internal standard was HMDS (δ 0.055 ppm). The IR spectra were recorded in the region 1500-3600 cm^{-1} on a Perkin-Elmer 580B instrument as nujol suspensions.

The compounds being studied were synthesized by known methods. Reactions were carried out in thick-walled glass vessels of volume 5 ml or in a 100 ml autoclave, in ethanol with an excess quantity of hydrazine hydrate. The reaction conditions and results are collated in Table 1.

Bis(3-methyl-4-pyrazolyl)methane (2a). A mixture of 3,5-diacetyl-1,4-dihydropyridine monohydrate (**1a**), hydrazine hydrate, and ethanol (see Table 1) was heated for 6 h at 140°C. The reaction mixture was evaporated, the colorless compound **2a** obtained was recrystallized from ethyl acetate–hexane. Yield 0.05 g (52%); mp 165-167°C. ^{1}H NMR spectrum, δ, ppm: 2.07 (6H, s, 3,3'-CH_3); 3.39 (2H, s, CH_2); 7.16 (2H, s, H-5,5'); 11.55-12.65 (2H, br. s, 1,1'-NH). Found, %: C 61.21; H 6.84; N 31.60. $C_9H_{12}N_4$. Calculated, %: C 61.34; H 6.86; N 31.79.

Bis(3,5-dimethyl-4-pyrazolyl)methane (2b) was obtained from 3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridine **1b** and was isolated after cooling the reaction mixture. The reaction also went well in dioxane (1 h at 140°C or 3 h on boiling).

Bis(3,5-dimethyl-4-pyrazolyl)-3-pyridylmethane (2c) was obtained from 3,5-diacetyl-2,6-dimethyl-4-(3-pyridyl)-1,4-dihydropyridine (**1c**) on cooling the reaction mixture. The colorless compound had mp 320°C (sublimes). ^{1}H NMR spectrum, δ, ppm: 1.70 (12H, s, 4CH_3); 5.26 (1H, s, CH); 7.20-7.50 (2H, m, H-4, H-5 Py); 8.25-8.45 (2H, m, H-2, H-6 Py); 11.92 (2H, br. s, NH). Found, %: C 68.26; H 6.82; N 24.86. $C_{16}H_{19}N_5$. Calculated, %: C 68.30; H 6.81; N 24.89.

2-Difluoromethoxyphenylbis(3,5-dimethyl-4-pyrazolyl)methane (2d) was obtained from 3,5-diacetyl-2,6-dimethyl-4-(2-difluoromethoxyphenyl)-1,4-dihydropyridine (**1d**). Colorless substance with mp 297-300°C. IR spectrum, ν, cm^{-1}: 3170, 3120, 3060, 3040 (NH), 1587, 1510. ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 1.67 (12H, s, 4CH_3); 5.35 (1H, s, CH); 7.02 (1H, t, *J* = 75, $OCHF_2$); 6.90-7.45 (4H, m, C_6H_4); 11.90 (2H, br. s, 2NH). Found, %: C 62.44; H 5.85; N 16.27. $C_{18}H_{20}F_2N_4O$. Calculated, %: C 62.42; H 5.82; N 16.17.

Bis(3,5-dimethyl-4-pyrazolyl)-3,4,5-trimethoxyphenylmethane (2e) was obtained from 3,5-diacetyl-2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyridine (**1e**). The colorless substance had mp 279-281°C (DMF–water). A portion of the substance was isolated from the cooled reaction mixture, and the remainder on evaporation. ^{1}H NMR spectrum, δ, ppm: 1.72 (12H, s, 3,5,3',5'-CH_3); 3.61 (9H, s, 3-CH_3O); 5.15 (1H, s, CH); 6.33 (2H, s, C_6H_2); 11.87 (2H, br. s, 2NH). Found, %: C 64.84; H 7.01; N 15.09. $C_{20}H_{26}N_4O_3$. Calculated, %: C 64.85; H 7.07; N 15.12.

Bis(5-methyl-3-phenyl-4-pyrazolyl)methane (2f) was obtained from 3,5-dibenzoyl-2,6-dimethyl-1,4-dihydropyridine **1f** after evaporation of the reaction mixture as a colorless substance of mp 146-148°C (ethyl acetate–hexane). ^{1}H NMR spectrum, δ, ppm: 1.84 (6H, s, 2CH_3); 3.80 (2H, s, CH_2); 7.10-7.60 (10H, m, 2C_6H_5); 10.5-12.5 (2H, br. s, NH). Found, %: C 76.45; H 6.15; N 17.13. $C_{21}H_{20}N_4$. Calculated, %: C 76.80; H 6.14; N 17.06.

Phenyl(3,5-dimethyl-4-pyrazolyl)(5'-methyl-3'-oxo-4'-pyrazolyl)methane (6) was obtained from 3-acetyl-5-ethoxycarbonyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine **5**. After evaporating the reaction mixture the residue was washed with acetone, mp 281-282°C (decomp.). IR spectrum, ν, cm^{-1}: 3310, 3160 (NH pyrazole), 2500-3120 (band with weakly expressed maxima at 3020-3120 and 2600-2700, NH pyrazolone), 1600, 1590, 1530, 1510. ^{1}H NMR spectrum, δ, ppm: 1.68 (3H, s, CH_3 pyrazolone); 1.73 (6H, s, 2CH_3 pyrazole); 5.13 (1H, s, CH); 6.95-7.50 (5H, m, C_6H_5); 10.00-11.50 (3H, br. s, 3NH). Found, %: C 67.96; H 6.50; N 19.62. $C_{16}H_{18}N_4O$. Calculated, %: C 68.06; H 6.43; N 19.84.

Bis(5-methyl-3-oxo-4-pyrazolyl)(3-pyridyl)methane (11) was obtained from 3,5-diethoxycarbonyl-2,6-dimethyl-4-(3-pyridyl)-1,4-dihydropyridine (**10**). Colorless substance with mp >300°C (decomp.). 5-Methyl-3-oxo-4-pyrazole **8** is formed as a side product. Compound **11** was isolated in 24% yield from the reaction

mixture in the reaction of 3-ethoxycarbonyl-2-methyl-5-oxo-4-(3-pyridyl)-1,4-dihydroindeno[1,2-*b*]pyridine (**14**) with hydrazine hydrate, together with the dihydrazone of 1,3-indanedione (**16**) (60% yield). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.08 (6H, s, $2CH_3$); 4.88 (1H, s, CH); 7.24 (1H, dd, J_1 = 8, J_2 = 4.5, H-5 Py); 7.54 (1H, dt, J_1 = 8, J_2 = 4.5, H-4 Py); 8.30-8.40 (2H, m, H-2, H-6 Py); 9.50-11.70 (4H, br. s, 4NH). Found, %: C 58.60; H 5.39; N 24.72. $C_{14}H_{15}N_5O_2$. Calculated, %: C 58.94; H 5.30; N 24.55.

3,5-Dimethyl-4-[α-(1,3-dihydrazono-2-indanyl)benzyl]pyrazole (15) was obtained from 5-oxo-4-phenyl-1,4-dihydroindeno[1,3-*b*]pyridine **12** on cooling the reaction mixture. Yellow crystalline substance of mp 165°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.70 (6H, s, $2CH_3$); 4.67 (1H, d, *J* = 2, 2-H indanyl); 4.92 (1H, br. s, C<u>H</u>C_6H_5); 6.40 (4H, s, $2NNH_2$); 7.00-7.80 (9H, m, C_6H_5 and 4,5,6,7-H indanyl); 10.90-11.55 (1H, br. s, NH pyrazole). After crystallization from ethanol: 1.05 (3H, m, *J* = 7, CH_3); 3.45 (2H, m, CH_2); 4.32 (1H, t, *J* = 5, OH). Found, %: C 68.49; H 6.82; N 21.05. $C_{21}H_{22}N_6 \cdot C_2H_5OH$. Calculated, %: C 68.29; H 6.92; N 20.79. An additional amount of compound **15** was obtained mixed with 1,3-indanedione dihydrazone (**16**) on evaporating the filtrate from the reaction mixture.

11-Phenyl-10H,12H-diindeno[1,2-*b*:2',1'-*e*]pyridine (19) was obtained from 10,12-dioxo-11-phenyl-5,10,11,12-tetrahydrodiindeno[1,2-*b*:2',1'-*e*]pyridine (**18**) after cooling the reaction mixture. Bright-yellow substance with mp 293-295°C. Found, %: C 90.41; H 5.20; N 4.15. $C_{25}H_{17}N$. Calculated, %: C 90.60; H 5.17; N 4.23.

3,5-Dimethyl-4-[α-thioureidobenzyl)pyrazole (21) was obtained from 5-acetyl-6-methyl-2-thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidine (**20**). After evaporating, the reaction mixture was stirred with ethyl acetate. Colorless crystalline solid **21** was precipitated; mp 189-191°C (acetone–ethyl acetate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.95 (6H, s, 3,5-CH_3); 6.60 (1H, d, *J* = 9, 4-CH); 6.90-7.45 (7H, m, C_6H_5 and NH_2); 8.05 (1H, d, *J* = 9, 4-β-NH); 10.05 (1H, br. s, 1-NH). Found, %: C 59.68; H 6.11; N 21.76. $C_{13}H_{16}N_4S$. Calculated, %: C 59.97; H 6.19; N 21.52.

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