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SYNTHESIS AND REACTIONS OF 1-(2-PYRIDYL)-3-METHYL-4-CHLORO-5-FORMYL-6,7-DIHYDROINDAZOLES

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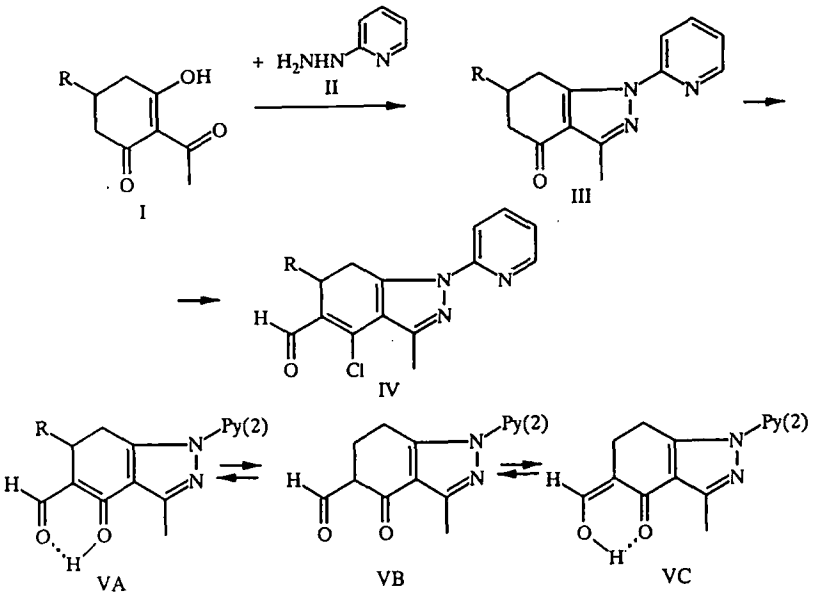
The Vilsmeier formylation of 1-(2-pyridyl)-3-methyl-4-oxo-4,5,6,7-tetrahydroindazole and its 6-phenyl derivative gives 1-(2-pyridyl)-3-methyl-4-chloro-5-formyl-6,7-dihydroindazoles. Reactions of these derivatives with different N- and C-nucleophilic agents, including bisnucleophiles, were studied as a means of obtaining new 4- and 5-functional derivatives of indazole and its condensed systems.

In the development of work on the modification of the carbocyclic part of 1-(2-pyridyl)-4,5,6,7-tetrahydroindazoles [1, 2], the formylation of 1-(2-pyridyl)-3-methyl-4-oxo-4,5,6,7-tetrahydroindazole (IIIa) and its 6-phenyl derivative (IIIb) was carried out.

Using the examples of 1-phenyl-4-oxo-4,5,6,7-tetrahydrobenzazoles [3-5], the dependence of the structure of the formylation products on the character of substitution at the $C_{(6)}$ atom was found previously, whereby the 6,6-disubstituted derivatives form 4-oxo-5-chloromethylene derivatives, and the 6-unsubstituted and 6-monosubstituted derivatives form 4-chloro-5-formyl-6,7-dihydrobenzazoles. The last are more reactive [6-9], and therefore we subjected just the indazoles (IIIa, b) to formylation. The indazoles (IIIa, b) were synthesized by the reactions of 2-acetyl-1,3-cyclohexanedione (Ia) and 2-acetyl-5-phenyl-1,3-cyclohexanedione (Ib) with 2-hydrazinopyridine (II). Formylation of the indazoles (IIIa, b) by the method of [3] leads to 1-(2-pyridyl)-3-methyl-4-chloro-5-formyl-6,7-dihydroindazoles with the yield of 85% for (IVa) and 65% for (IVb). The frequency of the carbonyl group in the IR spectra of these β-chlorovinylaldehydes (the IR and PMR spectral data are presented in Table 1) is observed at 1660-1654 cm^{-1}, and the signal of the proton of the aldehyde function is characterized by the chemical shift of 10.18-10.20 ppm in the PMR spectra.



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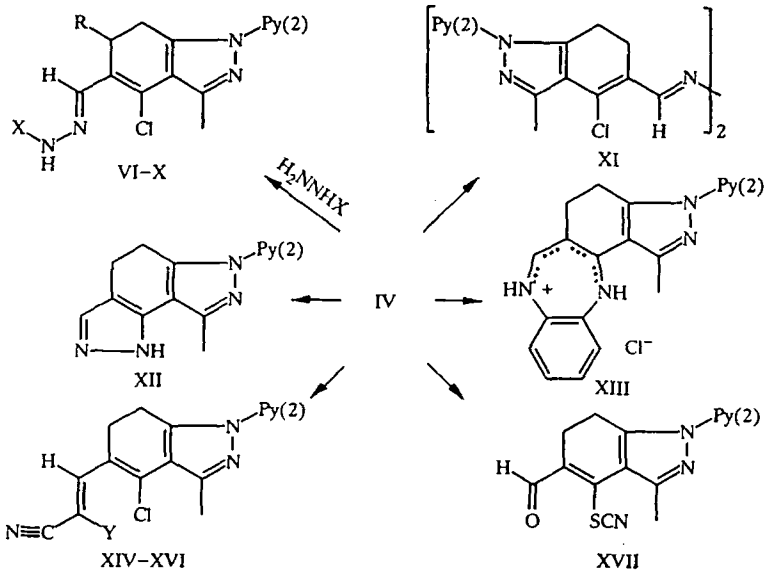

I, III, IV, VI—X a R = H; b R = C_6H_5; VI X = C_6H_5; VII X = $C_5H_4N(2)$; VIII X = CO—$C_5H_4N(4)$; IX X = CO—$C_6H_4OH(2)$; X X = $SO_2C_6H_4CH_3(4)$; XIV Y = $COOC_2H_5$; XV Y = $CONH_2$; XVI Y = CN

The boiling of the dihydroindazole (IVa) in the aqueous-ethanolic solution of sodium hydroxide results in its hydrolysis to the ketoaldehyde, for which three tautomeric forms (VA-C) are allowable. In the IR spectrum of compound (V) above 1600 cm^{-1}, only one absorption maximum is found at 1648 cm^{-1}, which excludes the structure (VB). The choice in favor of (VC) was made on the basis of the PMR spectrum in which the doublet signal of the methylene proton is observed at 7.27 ppm, and the doublet signal of the hydroxyl proton involved in the intramolecular hydrogen bond is observed at 13.81 ppm. The reaction of the β-chlorovinylaldehydes (IV) with a series of N- and C-nucleophiles was investigated. The corresponding 5-hydrazonomethyl derivatives (VI)-(X) were obtained in the reactions with phenyl- and 2-pyridylhydrazines, and hydrazides of isonicotinic acid, salicylic acid, and p-toluenesulfonic acid.

Reaction of the β-chlorovinylaldehyde (IVa) with hydrazine hydrate using the reagent molar ratio of both 2:1 and 1:1 only leads to the formation of the azine (XI), and the boiling in ethanol with hydrazine hydrochloride in the presence of potassium carbonate leads to 6-(2-pyridyl)-8-methyl-4,5-dihydro-1H-indazolo[4,5-c]pyrazole (XII).

Reaction of the chlorovinylaldehyde (IVa) with o-phenylenediamine leads to 1-methyl-3-(2-pyridyl)-4,5-dihydro-7H-benzo[b]indazolo[4,5-e][1,4]diazepine hydrochloride (XIII), in the PMR spectrum of which the signals of the protons of the NH groups are observed at 9.09 and 10.09 ppm.

Reactions of the chlorovinylaldehyde (IVa) with ethyl cyanoacetate and cyanacetamide, as well as malonodinitrile, were performed in the presence of triethylamine. The structure of the resulting 4-chloro-5-ethenyl-6,7-dihydroindazoles (XIV)-(XVI) was confirmed by the combination of IR and PMR spectral data. Thus, the ester carbonyl of compound (XIV) is characterized by the frequency 1726 cm^{-1}, and the amide carbonyl of (XV) is characterized at 1698 cm^{-1}. The vibration frequencies of the nitrile groups of compounds (XIV)-(XVI) are observed in the range of 2220-2208 cm^{-1}, and the chemical shift of the proton at the $C_{(1)}$ atom of the ethenyl group is observed at 8.27-8.56 ppm.

The reaction of (IVa) with potassium thiocyanate leads to the 4-thiocyanato-5-formyl derivative (XVII), the structure of which was confirmed by spectral data (ν_{SCN} 2160 cm^{-1}; δ_{CHO} 10.38 ppm).

EXPERIMENTAL

The IR spectra were taken on the Specord-75 IR spectrometer using suspensions of substances in mineral oil (1800-1500 cm^{-1}) and hexachlorobutadiene (3600-2000 cm^{-1}). The vibration frequencies of the C–H bonds in the region of 3050-2800 cm^{-1} were not indicated. The PMR spectra were taken in $CDCl_3$ and DMSO-D_6 on the Bruker WH-90/DS spectrometer (90 MHz) with the internal standard TMS.

TABLE 1. IR and PMR Spectra of the Compounds Synthesized

Compound	IR spectrum, cm^{-1}	PMR spectrum, ppm
IIIa	1668, 1614, 1576, 1562, 1540	($CDCl_3$). 2,24 (2H, m,); 2,50 (2H, t, J = 7 Hz, CH_2); 2,51 (3H, s, CH_3); 3,42 (2H, t, J = 7 Hz, CH_2); 7,24 (1H, m, C_5H_4N); 7,82 (2H, m, C_5H_4N); 8,44 (1H, m, C_5H_4N)
IIIb	1672, 1590, 1578, 1562	($CDCl_3$). 2,56 (3H, s, CH_3); 2,78...3,87 (5H, m, $2CH_2$, CH); 7,27...8,38 (4H, m, C_5H_4N)
IVa	1654, 1600, 1580, 1532	($CDCl_3$). 2,56 (3H, s, CH_3); 2,80 (2H, t, J = 8 Hz, CH_2); 3,42 (2H, t, J = 8 Hz, CH_2); 7,18 (1H, m, C_5H_4N); 7,8 (2H, m, C_5H_4N); 7,18...8,38 (4H, m, C_5H_4N); 10,18 (1H, s, CHO)
IVb	1660, 1605, 1578, 1535	($CDCl_3$). 2,58 (3H, s, CH_3); 3,56 (1H, d. d, J = 18, J = 9 Hz 7-H'); 4,09 (1H, d. d, J = 18, J = 2 Hz, 7-H''); 4,53 (1H, d. d, J = 9, J = 2 Hz, 6-H); 7,18 (6H, center m, C_6H_5); 7,19 (1H, m, C_5H_4N); 7,8 (2H, m, C_5H_4N); 8,36 (1H, m, C_5H_4N); 10,20 (1H, s, CHO)
Vc	1648, 1594, 1562, 1542	($CDCl_3$). 2,04...2,11 (5H, m, CH_2, CH_3); 2,77 (2H, t, J = 7 Hz, CH_2); 7,20...8,42 (4H, m, C_5H_4N); 7,27 (1H, d, J = 8 Hz, —CH—); 13,81 (1H, br.d., J = 8 Hz, OH)
VIa	1606, 1598, 1582, 1556, 1520; 3300	($CDCl_3$). 2,56 (3H, s, CH_3); 3,02 (2H, t, CH_2); 3,40 (2H, t, CH_2); 7,16...8,40 (11H, m, C_6H_5, C_5H_4N, —CH—, NH)
VIb	1626, 1606, 1598, 1564; 3320	($CDCl_3$). 2,56 (3H, s, CH_3); 3,56 (1H, d. d, J = 18, J = 9 Hz, 7-H'); 4,05 (1H, d. d, J = 18, J = 2 Hz, 7-H''); 4,84 (1H, d. d, J = 9, J = 2 Hz, 6-H); 7,04...7,82 (14H, m, $2C_6H_5$, C_5H_4N, —CH—); 7,87 (1H, NH); 8,29 (1H, m, C_5H_4N)
VIIa	1654, 1606, 1564, 1535; 3400	($CDCl_3$). 2,51 (3H, s, CH_3); 3,19 (2H, t, J = 7 Hz, CH_2); 3,42 (2H, t, J = 7 Hz, CH_2); 7,11...8,44 (9H, m, $2C_5H_4N$, —CH—); 12,94 (1H, br. s, NH)
VIIIa	1660, 1586, 1554, 1540; 3170	(DMSO-D_6). 2,49 (3H, s, CH_3); 2,93 (2H, t, J = 7 Hz, CH_2); 3,40 (2H, t, J = 7 Hz, CH_2); 7,40...8,79 (8H, m, $2C_5H_4N$); 8,78 (1H, s, —CH—); 12,09 (1H, br. s, NH)
IXa	1630, 1588, 1550; 3240, 2700, 2600	(DMSO-D_6). 2,50 (3H, s, CH_3); 2,91 (2H, m, CH_2); 3,33 (2H, m, CH_2); 6,93...8,71 (8H, m, C_5H_4N, C_6H_4); 8,71 (1H, s, —CH—); 11,91 (2H, br. s, NH, OH)
Xa	1596, 1578, 1538, 3180	($CDCl_3$). 2,38 (3H, s, CH_3); 2,47 (3H, s, CH_3); 2,76 (2H, t, J = 7 Hz, CH_2); 3,33 (2H, t, J = 7 Hz, CH_2); 7,27...8,38 (8H, m, C_5H_4N, C_6H_4); 8.13 (1H, s, —CH—); 10,76 (1H, br. s, NH)
XI	1590, 1580, 1570; 1538	(HMP). 2,26 (6H, s, $2CH_3$); 3,09 (4H, t, J = 7 Hz, CH_2); 3,47 (4H, t, J = 7 Hz, CH_2); 7,49 (2H, m, C_5H_4N); 7,96...8,24 (4H, m, C_5H_4N); 8,56 (2H, m, C_5H_4N); 9,13 (2H, s, —CH—)
XII	1594, 1574, 1530; 3200, 3080	($CDCl_3$). 2,48 (3H, s, CH_3); 2,79 (2H, t, J = 7 Hz, CH_2); 3,42 (2H, t, J = 7 Hz, CH_2); 7,08 (1H, m, C_5H_4N); 7,26...7,75 (3H, m, C_5H_4N, —CH—); 8,31 (1H, m, C_5H_4N); 11,86 (1H, NH)
XIII	1638, 1620, 1594, 1544, 1514, 1500; 3170, 2900...2750	(DMSO-D_6). 2,41 (2H, t, J = 7 Hz, CH_2); 2,6 (3H, s, CH_3); 3,18 (2H, t, J = 7 Hz, CH_2); 6,62...8,47 (9H, m, C_6H_4, C_6H_5N, —CH—); 9,09 (1H, NH); 10,1 (1H, NH)
XIV	1726, 1594, 1580, 1546, 1514; 2216	($CDCl_3$). 1,37 (3H, t, J = 7 Hz, CH_3); 2,56 (3H, s, CH_3); 3,38 (4H, center m, CH_2—CH_2); 4,36 (2H, q, J = 7 Hz, —O—CH_2); 7,22 (1H, m, C_6H_4N); 7,84 (2H, center m, C_5H_4N); 8,42 (1H, m, C_5H_4N); 8,56 (1H, s, —CH—)
XV	1698, 1622, 1600, 1578, 1550, 1530; 3430, 3330, 3280, 3220, 2208	(DMSO-D_6). 2,55 (3H, s, CH_3); 3,27...3,47 (4H, m, CH_2—CH_2); 7,40...8,49 (4H, m, C_5H_4N); 8,27 (1H, d, J = 2 Hz, —CH—); 7,68 (2H, br. s, NH_2)
XVI	1598, 1565, 1550, 1506; 2220, 2208	(DMSO-D_6). 2,55 (3H, s, CH_3); 3,20 (2H, t, J = 8 Hz, CH_2); 3,51 (2H, t, J = 8 Hz, CH_2); 7,24...8,42 (5H, m, C_5H_4N, —CH—)
XVII	1658, 1584, 1572, 1526; 2160	(DCDCl$_3$). 2,76 (3H, s, CH_3); 2,84 (2H, t, J = 7 Hz, CH_2); 3,44 (2H, t, J = 7 Hz, CH_2); 7,22 (1H, m, C_5H_4N); 7,89 (2H, m, C_5H_4N); 8,4 (1H, m, C_5H_4N); 10,38 (1H, s, CHO)

General methods for the synthesis of compounds of the same type are presented. The yield, melting temperature, empirical formula, and data of the elemental analysis are presented in Table 2.

6H- and 6-Phenyl-1-(2-pyridyl)-3-methyl-4-oxo-4,5,6,7-tetrahydroindazoles (IIIa, b). The mixture of 25 mmole of 2-acetyl-1,3-cyclohexanedione (Ia) or (Ib) and the equimolar amount of 2-hydrazinopyridine (II) is boiled for 3 h in 250 ml of ethanol in the presence of 1 ml of concentrated HCl. The mixture is held for 24 h in a refrigerator, and the precipitated indazoles (III) are filtered off and recrystallized from ethanol.

6-H and 6-Phenyl-1-(2-pyridyl)-3-methyl-4-chloro-5-formyl-6,7-dihydroindazoles (IVa, b). Into the suspension of 3.0 mmole of the 4-oxo-4,5,6,7-tetrahydroindazoles (IIIa, b) in 10 ml of DMF is poured, with stirring, the solution of 0.8 ml (9.0 mmole) of phosphorus oxychloride in 4 ml of DMF. The mixture is heated for 1 h on a boiling water bath, cooled, and poured onto ice. The residue of (IV) is filtered off and recrystallized from ethanol.

TABLE 2. Characterization of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %					mp, °C	Yield, %
		C	H	N	Cl	S		
IIIa	$C_{13}H_{13}N_3O$	68,61 / 68,70	5,65 / 5,76	18,56 / 18,49			180...181	65
IIIb	$C_{19}H_{17}N_3O$	75,35 / 75,22	5,60 / 5,65	13,70 / 13,85			148...151	70
IVa	$C_{14}H_{12}ClN_3O$	61,55 / 61,43	4,40 / 4,42	15,43 / 15,35	12,90 / 12,95		117...118	85
IVb	$C_{20}H_{16}ClN_3O$	68,50 / 68,67	4,51 / 4,61	12,13 / 12,01	10,30 / 10,13		169...171	65
V	$C_{14}H_{13}N_3O_2$	65,80 / 65,87	5,05 / 5,13	16,28 / 16,46			116...118	60
VIa	$C_{20}H_{18}ClN_5$	65,88 / 66,02	5,03 / 4,99	19,30 / 19,25	9,55 / 9,74		199...200	76
VIb	$C_{26}H_{22}ClN_5$	70,77 / 70,98	5,11 / 5,04	15,80 / 15,92	8,20 / 8,06		202...204	60
VIIa	$C_{19}H_{17}ClN_6$	62,42 / 62,55	4,58 / 4,70	23,00 / 23,04	9,53 / 9,72		>270 (subl.)	82
VIIIa	$C_{20}H_{17}ClN_6O$	61,01 / 61,15	4,30 / 4,36	21,20 / 21,39	8,85 / 9,02		244...246	77
IXa	$C_{21}H_{18}ClN_5O_2$	61,84 / 61,77	4,45 / 4,42	17,17 / 17,17	8,69 / 8,63		234...236	95
Xa	$C_{21}H_{20}ClN_5O_2S$	57,15 / 57,33	4,01 / 4,12	16,05 / 15,92	8,18 / 8,06	7,40 / 7,29	217...219	77
XI	$C_{28}H_{24}Cl_2N_8$	61,68 / 61,88	4,40 / 4,45	20,83 / 20,62	13,25 / 13,05		274...275	54
XII	$C_{14}H_{13}N_5$	66,70 / 66,91	5,15 / 5,21	27,70 / 27,87			193...194	95
XIII	$C_{20}H_{18}ClN_5$	65,88 / 66,02	5,03 / 4,99	19,05 / 19,25	9,88 / 9,74		211...215	86
XIV	$C_{19}H_{17}ClN_4O_2$	61,87 / 61,68	4,65 / 4,65	15,19 / 15,15	9,61 / 9,59		177...179	76
XV	$C_{17}H_{14}ClN_5O$	60,24 / 60,09	4,14 / 4,15	20,42 / 20,61	10,40 / 10,43		258...260	67
XVI	$C_{17}H_{12}ClN_5$	63,30 / 63,45	3,88 / 3,76	21,70 / 21,76	10,91 / 11,02		220...222	23
XVII	$C_{15}H_{12}N_4OS$	60,60 / 60,79	3,91 / 4,08	18,80 / 18,91		10,66 / 10,82	145...146	75

1-(2-Pyridyl)-3-methyl-4-oxo-5-hydroxymethylene-4,5,6,7-tetrahydroindazole (VC). To the solution of 0.55 g (2.0 mmole) of the chlorovinylketone (IVa) in 10 ml of ethanol are added 2.4 ml of the 10% aqueous solution of sodium hydroxide (6.0 mmole), and the mixture is boiled for 30 min. The cooled solution is poured into 60 ml of water prior to filtration. The filtrate is neutralized with diluted (1:1) hydrochloric acid to the pH 6-7. The precipitated colorless residue is filtered off after 2 h and recrystallized from 50% ethanol.

6-H- and 6-Phenyl-1-(2-pyridyl)-3-methyl-4-chloro-5-phenylhydrazonomethyl-6,7-dihydroindazoles (VIa,b). To the hot solution of 1.6 mmole of the chlorovinylaldehyde (IVa, b) in 15 ml of ethanol is added 0.16 ml (1.6 mmole) of phenylhydrazine, and the mixture is boiled for 1 h. The mixture is cooled and diluted with 15 ml of water. Filtration is performed after 24 h, and recrystallization is performed from ethanol.

5-(2-Pyridylhydrazonomethyl)-, 5-Isonicotinoylhydrazonomethyl-, 5-Salicylhydrazonomethyl-, and 5-Tosylhydrazonomethyl-1-(2-pyridyl)-3-methyl-4-chloro-6,7-dihydroindazoles (VII)-(X). To the hot solution of 0.82 g (3 mmole) of 1-(2-pyridyl)-3-methyl-4-chloro-5-formyl-6,7-dihydroindazole (IVa) in 10 ml of ethanol is added the hot solution of 3.0 mmole, correspondingly, of 2-pyridylhydrazine, isonicotinoylhydrazine, 2-salicyloylhydrazine, and tosylhydrazine in 15 ml of hot ethanol, and the mixture is boiled for 5 min in the case of (VII) and (IX), and for 30 min in the case of (VIII) and (X). The mixture is cooled, and the precipitated residue is filtered off prior to the recrystallization of (XII) and (IX) from DMF, and (VIII) and (X) from ethanol.

6-(2-Pyridyl)-8-methyl-4,5-dihydro-1H-indazolo[4,5-c]pyrazole (XII). The mixture of 0.54 g (2.0 mmole) of (IVa), 0.42 g (4.0 mmole) of hydrazine hydrochloride, and 0.85 g (8.0 mmole) of potassium carbonate is boiled for 2 h in 15 ml of abs. ethanol. After cooling the mixture, 40 ml of water are added. After 24 h, (XII) is filtered off and recrystallized from 50% ethanol.

C,C′-Di[1-(2-pyridyl)-3-methyl-4-chloro-5-indazolyl]methanalazine (XI). To the solution of 0.54 g (2.0 mmole) of (IVa) in 15 ml of ethanol at 60-70°C is added, with stirring, the solution of 0.10 g (2.0 mmole) of hydrazine hydrate in 10

ml of ethanol. The reaction mixture solidifies quickly. The yellow azine is filtered off and washed on the filter with hot ethanol prior to recrystallization from DMF.

1-Methyl-3-(2-pyridyl)-4,5-dihydro-7H-benzo[b]indazolo-[4,5-e]1,4-diazepine Hydrochloride (XIII). The reaction mixture of 0.27 g (1.0 mmole) of (IVa), 0.11 g (1.0 mmole) of o-phenylenediamine, and 0.4 ml of concentrated hydrochloric acid in 10 ml of abs. ethanol is boiled for 5 min. The reaction mixture is cooled, and dark violet crystals of the hydrochloride (XIII) are filtered off. The crystals are washed on the filter with a small amount of hot abs. ethanol and then with diethyl ether.

5-(2-Cyano-2-ethoxycarbonylethenyl-, 5-(2-Cyano-2-aminocarbonylethenyl-, and 5-(2,2-Dicyanoethenyl)-1-(2-pyridyl)-3-methyl-4-chloro-6,7-dihydroindazoles (XIV)-(XVI). The reaction mixture of 0.54 g (2.0 mmole) of (IVa), 0.20 g (2 mmole) of triethylamine, and 2.0 mmole, correspondingly, of ethyl cyanoacetate, cyanoacetamide, and malonodinitrile in 15 ml of abs. ethanol is stirred for 2 h at 20°C in the cases of (XIV) and (XVI), and boiled for 2 h in the case of (XV). The mixtures are placed for 24 h in a refrigerator, and the residue is filtered off and recrystallized from ethanol in the case of (XIV), acetic acid in the case of (XV), and DMF–ethanol in the case of (XVI).

1-(2-Pyridyl)-3-methyl-4-thiocyanato-5-formyl-6,7-dihydroindazole (XVII). The mixture of 0.54 g of potassium thiocyanate in 15 ml of ethanol is boiled for 2 h. The ethanol is distilled off on a rotary evaporator. To the oil-forming residue are added 20 ml of water. Filtration is performed after 24 h, and (XVII) is recrystallized from ethanol.

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