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SYNTHESES BASED ON 4-CHLORO-1-[3,5-DI(TRIFLUORO-METHYL)PHENYL]-, 4-CHLORO-1-(2,4-DIFLUOROPHENYL)-5-FORMYL-3-METHYL-6,7-DIHYDROINDAZOLES, AND 4-CHLORO-5-FORMYL-3-METHYL-1-(2-PYRIDYL)-6,7-DIHYDROINDAZOLES

I. Strakova, A. Strakovs, and M. Petrova

Vilsmeier formylation of 1-[3,5-di(trifluoromethyl)phenyl]- and 1-(2,4-difluorophenyl)-3-methyl-4-oxo-4,5,6,7-tetrahydroindazoles gave the corresponding 1-aryl-4-chloro-5-formyl-3-methyl-6,7-dihydroindazoles. Reaction of the latter with amidines, o-phenylenediamine, hydrazine, or hydroxylamine gave a series of 1-aryl-3-methyl-6,6-dihydroindazoles annelated at positions 4 and 5. The reaction of 4-chloro-5-formyl-3-methyl-1-(2-pyridyl)-6,7-dihydroindazole with substituted anilines gave 5-arylaminomethylene-4-oxo- or 5-arylaminomethylene-4-arylimino-3-methyl-1-(2-pyridyl)-4,5,6,7-tetrahydroindazoles depending on the molar ratio of reagents and the nucleophilicity of the amines.

Keywords: β-arylaminovinyl ketones, β-arylaminovinylarylimines, 4,5-dihydro-7H-benzo[*b*]indazolo-[4,5-*e*]diazepines, 4,5-dihydro-1H-pyrazolo[3,4-*e*]indazoles, 3,8-substituted 4,5-dihydropyrazolo[5,4-*h*]-quinazolines, β-chlorovinylaldehydes.

Modification of indazoles hydrogenated in the carbocycle is mostly carried out with the aim of finding biologically active compounds [1-6]. Continuing our research in this direction [7-11] we report in this work the synthesis of a series of novel compounds of the group indicated. Hence the Vilsmeier formylation of 1-[3,5-di(trifluoromethyl)phenyl]- (**1**) and 1-(2,4-difluorophenyl)-3-methyl-4-oxo-4,5,6,7-tetrahydroindazole (**2**) gave the corresponding β-chlorovinylaldehydes **3** (75%) and **4** (86%). The method is given in [7].

The starting indazole **1** is reported in [10] and the indazole **2** has been synthesized for the first time from 2-acetyl-1,3-cyclohexanedione and 2,4-difluorophenylhydrazine. The structure of the products **3** and **4** is confirmed from spectroscopic data (Table 1). In the IR spectra of compounds **3** and **4** the carbonyl group band is seen at 1653 and 1659 cm^{-1} and in the ^1H NMR spectra the aldehyde proton signals are observed at 10.40 and 10.20 ppm respectively. Refluxing the aldehydes **3**, **4** with guanidine carbonate, benzamidine, 4-pyridylcarbamidine, 5-trifluoromethyl-2-pyridylcarbamidine hydrochlorides, or the hydrobromides of 1-pyrrolidinyl- and 4-morpholinylcarbamidines in ethanol in the presence of sodium ethylate (or KOH in the case of the pyrrolidine and morpholine carbamidines) gave the corresponding 3,8-disubstituted 1-methyl-4,5-dihydropyrazolo[5,4-*h*]quinazolines **5-13**.

Refluxing the aldehydes **3** and **4** for a short time with *o*-phenylenediamine in ethanol in the presence of conc. HCl gave the corresponding 3-substituted 1-methyl-4,5-dihydro-7H-benzo[*b*]indazolo[4,5-*e*][1,4]diazepine hydrochlorides **14**, **15**, the ^1H NMR spectra of which showed an N^+H group proton signal at 9.50 and 10.32 or 9.36 and 10.30 ppm respectively.

Riga Technical University, Riga LV-1658, Latvia, e-mail: marina@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 740-750, May, 2005. Original article submitted May 14, 2003.

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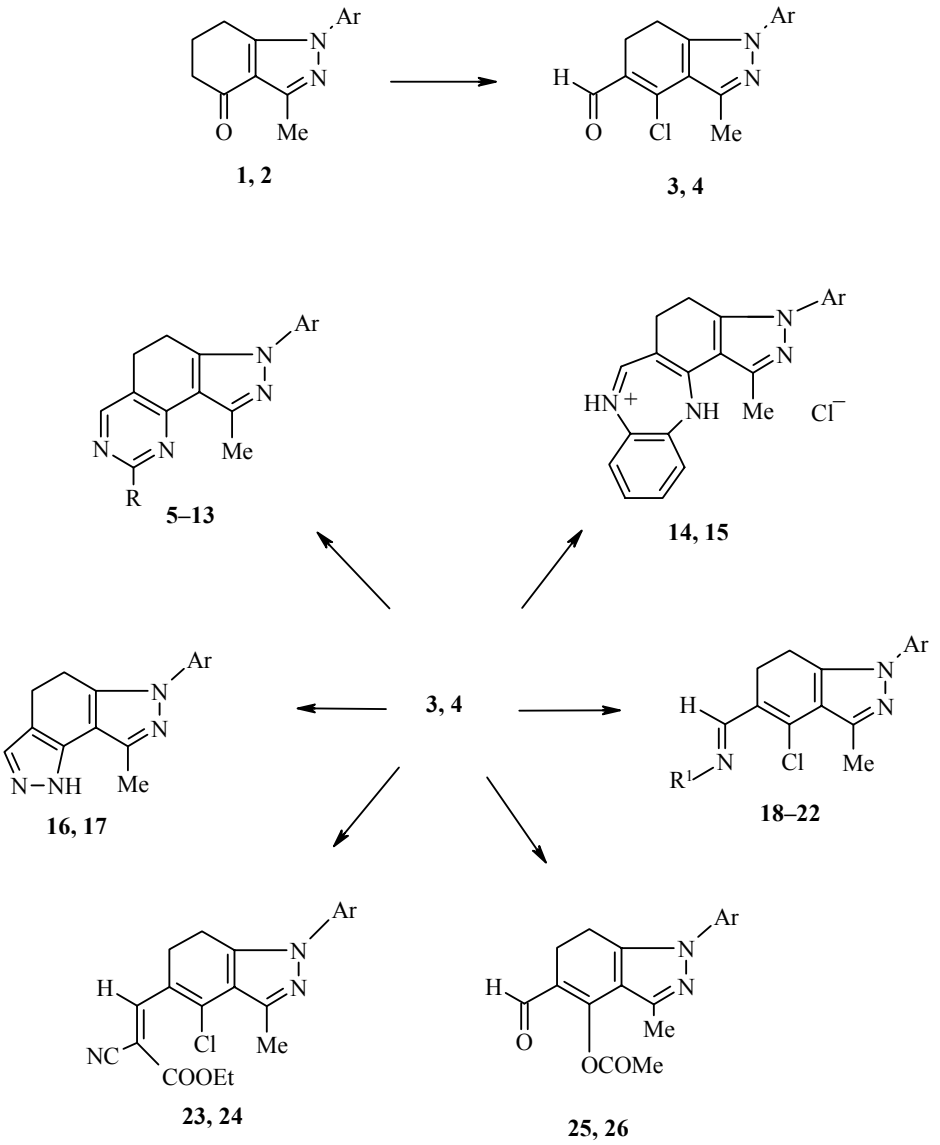
Scheme 1



1, **3**, **5-9**, **14**, **16**, **18**, **19**, **23**, **25** Ar = 3,5-$(CF_3)_2C_6H_3$; **2**, **4**, **10-13, 15, 17**, **20-22**, **24**, **26** Ar = 2,4-$F_2C_6H_3$; **5**, **10** R = NH_2; **6**, **12** R = 4-C_5H_4N; **7** R = 4-$CF_3C_5H_3N$-2; **8**, **13** R = $(CH_2)_4N$; **11** R = Ph; **9** R = $O(CH_2CH_2)_2N$; **18**, **20** R^1= OH; **19**, **21** R^1 = 3,5-$(CF_3)_2C_6H_3NH$; **22** R^1 = EtOOCNH

Refluxing the aldehydes **3** and **4** with hydrazine hydrochloride in the presence of potassium carbonate in ethanol for 3 h gave the 6-substituted 4,5-dihydro-1H-pyrazolo[3,4-*e*]indazoles **16** and **17** respectively, refluxing with hydroxylamine hydrochloride in pyridine the oximes **18** and **20**, with 3,5-di(trifluoromethyl)-phenylhydrazine in ethanol the hydrazones **19** and **21**, and refluxing aldehyde **4** with carbethoxyhydrazine the hydrazone **22**.

Treatment of the aldehydes **3** and **4** with ethyl cyanoacetate in absolute ethanol in the presence of diethylamine at 20°C gave the corresponding 1-substituted 4-chloro-5-(2-cyano-2-carbethoxyethenyl)-3-methyl-6,7-dihydroindazoles **23** and **24**. The ester groups of these compounds show characteristic bands for C=O groups at 1713 and 1717 cm^{-1}, a CN group at 2220 cm^{-1}, and an ethylene proton at 8.58 ppm.

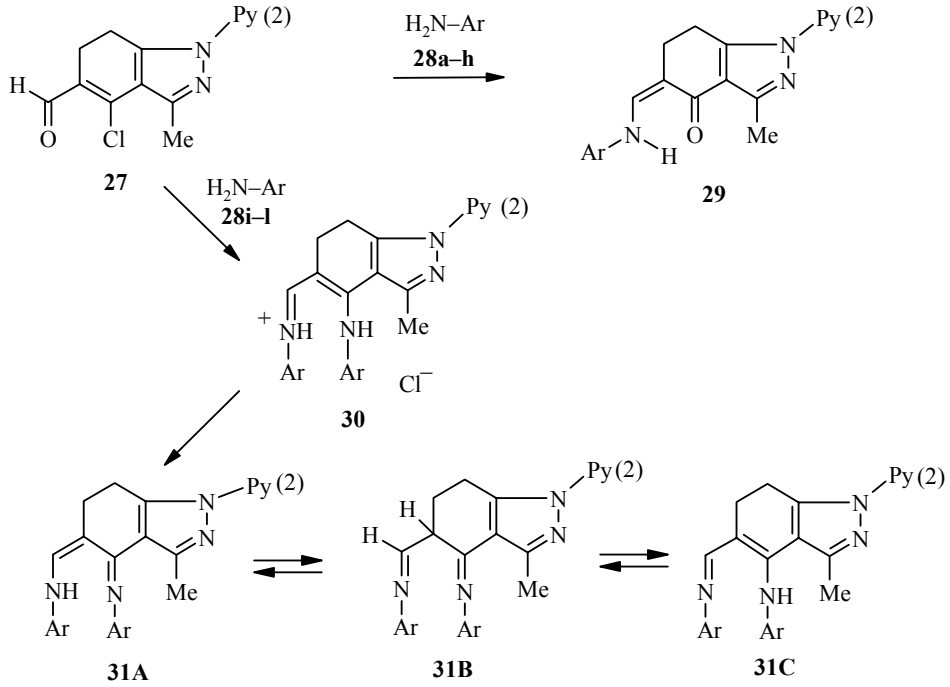
Refluxing the aldehydes **3** and **4** in acetic anhydride gave the 4-acetoxy derivatives **25** and **26**, the carbonyl function frequencies of which appear at 1777 and 1681 and 1775 and 1685 cm^{-1} respectively.

To extend the investigation of 4-chloro-5-formyl-3-methyl-1-(2-pyridyl)-6,7-dihydroindazole (**27**) [7, 8] we have now studied the reaction with aniline derivatives of different nucleophilicities **28a-l**.

When carrying out the reactions both with an equimolar amount of reagents and also with an excess of amine, the anilines of lower basicity **28a-h** ($pK_{BH}^{+} < 3.5$) gave the corresponding 5-arylaminomethylene-3-methyl-4-oxo-1-(2-pyridyl)-4,5,6,7-tetrahydroindazoles **29a-h**. Under these reaction conditions the equimolar amount of water separated in the reaction of the formyl group with the amine is sufficient to hydrolyze the $C_{(4)}$–Cl bond.

With a twofold excess of more nucleophilic amines **28i-l** relative to the indazole **27** the 5-arylaminomethylene-4-arylimino-4,5,6,7-tetrahydroindazole hydrochlorides **30i-l** are formed. Reaction of compound **27** with amines **28a,b** in the molar ratio 1:2 also gives the corresponding hydrochlorides **30a,b**. Treatment of a suspension of the hydrochlorides **30a,b,i-l** in ethanol with a 10% aqueous solution of $NaHCO_3$ gave the 4-arylamino-5-arylaminomethylene-4,5,6,7-tetrahydroindazoles **31a,b,i-l**.

Scheme 2



28-31 a Ar = C_6H_4Cl-2; **b** Ar = $C_6H_4CF_3$-3; **c** Ar = C_6H_4COOH-2; **d** Ar = C_6H_4COO Me-2; **e** Ar = $C_6H_2Br_3$-2,4,6; **f** Ar = $C_6H_2Cl_3$-2,4,6; **g** Ar = $C_6H_4NO_2$-3; **h** Ar = $C_6H_4NO_2$-4; **i** Ar = C_6H_5; **j** Ar = C_6H_4OMe-4; **k** Ar = C_6H_4Me-4; **l** Ar = C_6H_4Br-4

Characteristic carbonyl group frequencies for the carbonyl groups of the ketones **29** are found in the region 1665-1646 and NH stretching vibrations at 3300-2800 cm^{-1}. In the IR spectra of the bases **31** the latter is of low intensity and detecting it is difficult. In the ^1H NMR spectra of the bases **31** the NH group proton has a chemical shift of 9-13 ppm and this confirms the presence of an H-chelated ring stabilized by intramolecular hydrogen bonding. The N^+–H group protons of the hydrochlorides **30** are also characterized by a low field chemical shifts (11-12 ppm) (Table 2).

Several of the synthesized arylaminomethylene ketones **29** (**29c,d,e**) are a mixture of isomers relative to the $C_{(5)}$=CHNH– double bond with the corresponding spectroscopic features.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Cl (Br)		
1	2	3	4	5	6	7	8
2	$C_{14}H_{12}F_2N_2O$	64.02 / 64.11	4.55 / 4.61	10.53 / 10.69		88-89	72
3	$C_{17}H_{11}ClF_6N_2O$	50.01 / 49.95	2.66 / 2.71	6.69 / 6.85	8.50 / 8.67	117-118	75
4	$C_{15}H_{11}ClF_2N_2O$	58.30 / 58.35	3.50 / 3.59	8.99 / 9.07	11.40 / 11.48	139-141	86
5	$C_{18}H_{13}F_6N_5$	52.13 / 52.30	3.20 / 3.17	16.82 / 16.95		191-192	61
6	$C_{23}H_{15}F_6N_5$	58.04 / 58.11	3.03 / 3.18	14.60 / 14.73		235-237	66
7	$C_{24}H_{14}F_9N_5$	52.92 / 53.05	2.55 / 2.60	12.92 / 12.89		247-249	48
8	$C_{22}H_{19}F_6N_5$	56.40 / 56.53	4.06 / 4.10	15.09 / 14.99		207-209	51
9	$C_{22}H_{19}F_6N_5O$	54.49 / 54.66	3.82 / 3.96	14.52 / 14.49		225-226	43
10	$C_{16}H_{13}F_2N_5$	61.11 / 61.33	4.25 / 4.18	22.43 / 22.36		232-234	57
11	$C_{22}H_{16}F_2N_4$	70.42 / 70.58	4.22 / 4.31	15.14 / 14.97		120-121	63
12	$C_{21}H_{15}F_2N_5$	67.02 / 67.18	4.09 / 4.03	18.55 / 18.66		238-239	62
13	$C_{20}H_{19}F_2N_5$	65.30 / 65.38	5.10 / 5.21	18.97 / 19.06		133-134	50
14	$C_{23}H_{17}ClF_6N_4$	55.20 / 55.37	3.34 / 3.44	11.11 / 11.23	6.90 / 7.11	315-320	79
15	$C_{21}H_{17}ClF_2N_4$	63.09 / 63.24	4.20 / 4.30	14.13 / 14.05	8.70 / 8.89	310-314	66
16	$C_{17}H_{12}F_6N_4$	52.65 / 52.85	3.01 / 3.13	14.40 / 14.50		171-172	49
17	$C_{15}H_{12}F_2N_4$	62.77 / 62.93	4.19 / 4.23	19.42 / 19.57		218-220	53
18	$C_{17}H_{12}ClF_6N_3O$	48.07 / 48.18	2.80 / 2.86	9.79 / 9.92	8.20 / 8.37	225-226	83
19	$C_{25}H_{15}ClF_{12}N_4$	47.40 / 47.30	2.31 / 2.38	8.70 / 8.83	5.40 / 5.58	225-226	88
20	$C_{15}H_{12}ClF_2N_3O$	55.49 / 55.65	3.62 / 3.74	13.03 / 12.98	10.80 / 10.95	200-202	80
21	$C_{23}H_{15}ClF_8N_4$	51.52 / 51.65	2.70 / 2.83	10.41 / 10.48	6.50 / 6.63	192-193	85
22	$C_{18}H_{17}ClF_2N_4O_2$	54.58 / 54.76	4.25 / 4.34	14.08 / 14.19	8.80 / 8.98	155-156	77
23	$C_{22}H_{16}ClF_6N_3O_2$	52.30 / 52.44	3.08 / 3.20	8.20 / 8.34	7.00 / 7.04	163-164	69
24	$C_{20}H_{16}ClF_2N_3O_2$	59.33 / 59.48	4.04 / 3.99	10.30 / 10.41	8.60 / 8.78	163-164	66
25	$C_{19}H_{14}F_6N_2O_3$	52.61 / 52.79	3.20 / 3.26	6.33 / 6.48		160-161	70
26	$C_{17}H_{14}F_2N_2O_3$	61.30 / 61.44	4.14 / 4.25	8.35 / 8.43		152-153	77
29a	$C_{20}H_{17}ClN_4O$	65.93 / 65.84	4.81 / 4.70	15.23 / 15.35	9.50 / 9.72	152-153	66
29b	$C_{21}H_{17}F_3N_4O$	63.10 / 63.31	4.22 / 4.30	14.14 / 14.06		174-175	50
29c	$C_{21}H_{18}N_4O_3$	67.10 / 67.37	4.90 / 4.85	14.73 / 14.96		269-271	75
29d	$C_{22}H_{20}N_4O_3$	67.86 / 68.03	5.16 / 5.19	14.42 / 14.42		138-140	64
29e	$C_{20}H_{15}Br_3N_4O$	42.14 / 42.36	2.70 / 2.67	10.02 / 9.88	42.40 / 42.27	222-224	46

TABLE 1 (continued)

1	2	3	4	5	6	7	8
29f	$C_{20}H_{15}Cl_3N_4O$	55.55 / 55.39	3.40 / 3.49	12.70 / 12.92	24.30 / 24.52	195-197	62
29g	$C_{20}H_{17}N_5O_3$	64.16 / 63.99	4.51 / 4.57	18.66 / 18.66		256-259	94
29h	$C_{20}H_{17}N_5O_3$	63.77 / 63.99	4.50 / 4.57	18.71 / 18.66		271-273	67
30a	$C_{26}H_{22}Cl_3N_5$	61.01 / 61.13	4.14 / 4.34	13.50 / 13.71	20.60 / 20.82	195-205	47
30b	$C_{28}H_{22}ClF_6N_5$	58.16 / 58.19	3.82 / 3.83	12.12 / 12.12		230-235	40
30i	$C_{26}H_{24}ClN_5$	70.70 / 70.66	5.51 / 5.47	15.78 / 15.84	8.20 / 8.02	207-210	95
30j	$C_{28}H_{28}ClN_5O_2$	67.05 / 66.99	5.61 / 5.62	14.03 / 13.95	7.10 / 7.06	235-240	90
30k	$C_{28}H_{28}ClN_5$	71.35 / 71.55	5.93 / 6.00	14.90 / 14.90	7.60 / 7.54	235-240	75
30l	$C_{26}H_{22}Br_2ClN_5$	51.94 / 52.07	3.58 / 3.70	11.58 / 11.68		226-230	83
31a	$C_{26}H_{21}Cl_2N_5$	65.60 / 65.83	4.41 / 4.46	14.58 / 14.76	15.20 / 14.95	161-162	78
31b	$C_{28}H_{21}F_6N_5$	61.91 / 62.11	3.90 / 3.91	12.81 / 12.93		145-147	71
31i	$C_{26}H_{23}N_5$	77.17 / 77.01	5.70 / 5.72	17.13 / 17.27		133-135	78
31j	$C_{28}H_{27}N_5O_2$	72.02 / 72.24	5.78 / 5.84	14.95 / 15.04		209-210	98
31k	$C_{28}H_{27}N_5$	77.40 / 77.57	6.11 / 6.28	16.03 / 16.15		133-135	99
31l	$C_{26}H_{21}Br_2N_5$	55.44 / 55.44	3.64 / 3.76	12.37 / 12.43	28.10 / 28.37	198-200	79

TABLE 2. IR and ^{1}H NMR Spectra of the Compounds Synthesized

Com-pound	IR spectrum, ν, cm^{-1} (C=O, NH, OH)	^{1}H NMR spectrum, δ, ppm (SSCC, *J*, Hz)
1	2	3
2	1667	**$CDCl_3$**. 2.14 (2H, m, CH_2); 2.47 (2H, m, CH_2); 2.51 (3H, s, CH_3); 2.74 (2H, m, CH_2); 7.03 (2H, center m, H_{Ar}); 7.47 (1H, center m, H_{Ar})
3	1653	**$CDCl_3$**. 2.58 (3H, s, CH_3); 2.85 (4H, center m, $2CH_2$); 7.90 (1H, br. s, H_{Ar}); 7.93 (2H, br. s, H_{Ar}); 10.40 (1H, s, CHO)
4	1659	**$CDCl_3$**. 2.50 (3H, s, CH_3); 2.72 (4H, center m, $2CH_2$); 6.89-7.54 (3H, m, H_{Ar}); 10.20 (1H, s, CHO)
5	3480, 3290, 3160-3100	**$CDCl_3$**. 2.63 (3H, s, CH_3); 2.94 (4H, m, $2CH_2$); 5.09 (2H, br. s, NH_2); 7.81 (1H, br. s, H_{Ar}); 7.98 (2H, br. s, H_{Ar}); 8.03 (1H, s, H-6)
6	1622	**DMSO-d_6**. 2.74 (3H, s, CH_3); 3.13 (4H, center m, $2CH_2$); 8.27 (5H, m, $3H_{Ar}$, $2H_{pyr}$); 8.76 (3H, m, $2H_{pyr}$, H-6)
7		**DMCO-d_6**. 2.67 (3H, s, CH_3); 3.28 (4H, center m, $2CH_2$); 8.26-9.21 (7H, m, $3H_{Ar}$, 3H , H-6)
8		**$CDCl_3$**. 2.01 (4H, center m, $2CH_2$); 2.72 (3H, s, CH_3); 2.96 (4H, center m, $2CH_2$); 3.63 (4H, center m, $N(CH_2)_2$); 7.85 (1H, br. s, H_{Ar}); 7.98 (2H, br. s, H_{Ar}); 8.12 (1H, s, H-6)
9		**$CDCl_3$**. 2.67 (3H, s, CH_3); 2.96 (4H, center m, $2CH_2$); 3.81 (8H, center m, $N(CH_2CH_2)_2O$); 7.92 (1H, br. s, H_{Ar}); 8.00 (2H, br. s, H_{Ar}); 8.16 (1H, s, H-6)
10	3400, 3300, 3150-3100	**$CDCl_3$** + **DMSO-d_6**. 2.61 (3H, s, CH_3); 2.78 (4H, m, $2CH_2$); 5.05 (2H, br. s, NH_2); 7.01 (2H, center m, H_{Ar}); 7.49 (1H, center m, H_{Ar}); 8.05 (1H, s, H-6)
11		**$CDCl_3$**. 2.85 (3H, s, CH_3); 2.92 (4H, center m, $2CH_2$); 7.01 (2H, m, H_{Ar}); 7.52 (3H, m, H_{Ph}); 7.56 (1H, m, H_{Ar}); 8.45 (1H, s, H-6); 8.46 (2H, m, H_{Ph})

TABLE 2 (continued)

1	2	3
12		**$CDCl_3$**. 2.78 (3H, s, CH_3); 2.94 (4H, br. s, $2CH_2$); 7.05 (2H, center m, H_{Ar}); 7.61 (1H, center m, H_{Ar}); 8.34 (2H, m, ^3J = 6.0, H_{pyr}); 8.54 (1H, s, H-6); 8.74 (2H, m, ^3J = 6.0, H_{pyr})
13		**$CDCl_3$**. 1.98 (4H, center m, $2CH_2$); 2.67 (3H, s, CH_3); 2.81 (4H, m, $2CH_2$); 3.64 (4H, center m, $N(CH_2)_2$); 7.01 (2H, center m, H_{Ar}); 7.52 (1H, center m, H_{Ar}); 8.07 (1H, s, H-6)
14	2850-2750	**DMCO-d_6**. 2.45 (2H, m, CH_2); 2.58 (3H, s, CH_3); 2.89 (2H, m, CH_2); 6.69 (2H, m, H_{Ar}); 6.85 (1H, d, ^3J = 8.0, H-6); 7.01 (2H, m, H_{Ar}); 8.22 (3H, m, H_{Ar}); 9.50 (1H, br. s, NH); 10.32 (1H, br. d, ^3J = 8.0, NH)
15	2850-2750	**DMSO-d_6**. 2.61 (3H, s, CH_3); 2.45 (4H, m, $2CH_2$); 6.72-7.74 (8H, m, $2H_{Ar}$, H-6); 9.36 (1H, br. s, NH); 10.30 (1H, d, ^3J = 8.0, NH)
16	3200, 3120	**$CDCl_3$**. 2.58 (3H, s, CH_3); 3.01 (4H, m, $2CH_2$); 7.38 (1H, s, H-6); 7.81 (1H, br. s, H_{Ar}); 8.01 (2H, br. s, H_{Ar}); 10.20 (1H, br. s, NH)
17	3200, 3100	**$CDCl_3$**. 2.53 (3H, s, CH_3); 2.77 (4H, center m, $2CH_2$); 6.97 (2H, center m, H_{Ar}); 7.28 (1H, s, H-3); 7.46 (1H, center m, H_{Ar}); 11.67 (1H, br. s, NH)
18	3280-3160	**$CDCl_3$**. 2.54 (3H, s, CH_3); 2.98 (4H, m, $2CH_2$); 7.85 (1H, br. s, H_{Ar}); 7.96 (2H, br. s, H_{Ar}); 8.34 (1H, s, N=CH–); 10.81 (1H, s, OH)
19		**$CDCl_3$**. 2.53 (3H, s, CH_3); 3.01 (4H, m, $2CH_2$); 7.21 (1H, br. s, H_{Ar}); 7.49 (2H, br. s, H_{Ar}); 7.83 (1H, br. s, H_{Ar}); 7.98 (2H, br. s, H_{Ar}); 8.16 (1H, s, N=CH–); 10.20 (1H, br. s, NH)
20	3330-3200	**$CDCl_3$** + **DMSO-d_6**. 2.49 (3H, s, CH_3); 2.76 (4H, center m, H_{Ar}); 7.03 (2H, center m, H_{Ar}); 7.49 (1H, center m, H_{Ar}); 8.38 (1H, s, N=CH); 10.34 (1H, br. s, OH)
21		**$CDCl_3$**. 2.52 (3H, s, CH_3); 2.89 (4H, center m, $2CH_2$); 6.81-7.35 (6H, m, H_{Ar}); 8.07 (2H, br. s, NH, N=CH–)
22	1722	**$CDCl_3$**. 1.27 (3H, t, ^3J = 7.0, CH_3); 2.52 (3H, s, CH_3); 2.65-3.01 (4H, m, $2CH_2$); 4.29 (2H, q, ^3J = 7.0, CH_2); 6.96 (2H, center m, H_{Ar}); 7.63 (1H, center m, H_{Ar}); 8.07 (1H, br. s, N=CH–); 8.09 (1H, br. s, NH)
23	1713; 2220	**$CDCl_3$**. 1.36 (3H, t, ^3J = 7.0, CH_3); 2.56 (3H, s, CH_3); 3.21 (4H, center m, $2CH_2$); 4.34 (2H, q, ^3J = 7.0, CH_2); 7.92 (1H, br. s, H_{Ar}); 7.95 (2H, br. s, H_{Ar}); 8.58 (1H, s, =CH–)
24	1717; 2220	**$CDCl_3$**. 1.35 (3H, t, ^3J = 7.0, CH_3); 2.55 (3H, s, CH_3); 2.79 (2H, t, ^3J = 7.0, CH_2); 3.22 (2H, t, ^3J = 7.0, CH_2); 4.35 (2H, q, ^3J = 7.0, CH_2); 7.02 (2H, center m, H_{Ar}); 7.48 (1H, center m, H_{Ar}); 8.58 (1H, s, =CH–)
25	1777; 3100	**$CDCl_3$**. 2.25 (3H, s, CH_3); 2.58 (3H, s, CH_3); 3.03 (4H, center m, $2CH_2$); 7.89 (1H, br. s, H_{Ar}); 7.96 (2H, br. s, H_{Ar}); 8.27 (1H, s, CHO)
26	1775, 1685	**$CDCl_3$**. 2.23 (3H, s, CH_3); 2.52 (3H, s, CH_3); 2.85 (4H, center m, $2CH_2$); 7.02 (2H, center m, H_{Ar}); 7.47 (1H, center m, H_{Ar}); 8.25 (1H, s, CHO)
29a	1655; 3200-2800	**DMSO-d_6**. 2.53 (3H, s, CH_3); 2.78 (2H, t, ^3J = 7, CH_2); 3.41 (2H, t, ^3J = 7, CH_2); 6.98 (1H, dt, ^3J = 8, ^4J = 1.5, C_6H_4); 7.25-8.09 (7H, m, C_6H_4, C_5H_4N, =CH–); 8.52 (1H, m, ^3J = 5, C_5H_4N); 11.65 (1H, d, ^3J = 13.5, NH)
29b	1658; 3200-2800	**DMSO-d_6**. 2.61 (3H, s, CH_3); 2.79 (2H, t, ^3J = 7, CH_2); 3.46 (2H, t, ^3J = 7, CH_2); 7.13-7.98 (8H, m, C_6H_4, C_5H_4N, =CH–); 8.42 (1H, m, ^3J =5, C_5H_4N); 11.49 (1H, d, ^3J = 11.4, NH)
29c	1680, 1656; 3200-2900	**DMSO-d_6**. 2.50 (3H, s, CH_3); 2.82 (2H, m, CH_2); 3.45 (2H, m, CH_2); 7.08-8.05 (8H, m, C_6H_4, C_5H_4N, =CH–); 8.45 (1H, m, ^3J = 5, C_5H_4N); 10.65 and 12.58 (1H, d, ^3J = 13, NH); 13.2 (1H, br. s, COOH)
29d	1716, 1665; 3300-3200	**$CDCl_3$**. 2.61 and 2.67 (3H, s, CH_3); 2.80 and 2.95 (2H, t, ^3J = 7, CH_2); 3.45 and 3.58 (2H, t, ^3J = 7, CH_2); 3.92 and 4.01 (3H, s, $COOCH_3$); 6.93 (1H, t, ^3J = 7, C_6H_4); 7.22-8.40 (8H, m, C_6H_4, C_5H_4N, =CH–); 10.61 and 12.95 (1H, d, ^3J = 13, NH)
29e	1646; 3200-2800	**$CDCl_3$**. 2.63 (3H, s, CH_3); 2.72 (2H, t, ^3J = 7, CH_2); 3.46 (2H, t, ^3J = 7, CH_2); 7.06 (1H, d, ^3J = 11, =CH–); 7.20 (1H, m, C_5H_4N); 7.49 (2H, s, C_6H_2); 7.81 (1H, d, ^3J = 8.4, ^4J = 1.7, C_5H_4N); 7.93 (1H, dt, ^3J = 8.4, $^{4,5}J$ = 1, C_5H_4N); 8.42 (1H, m, ^3J = 5, C_5H_4N); 11.40 (1H, d, ^3J = 11, NH)
29f	1650; 3200-2800	**DMSO-d_6**. 2.52 (3H, s, CH_3); 2.81 (2H, m, CH_2); 3.43 (2H, m, CH_2); 7.29-8.09 (6H, m, C_6H_2, C_5H_4N, =CH–); 8.50 (1H, m, ^3J = 5, C_5H_4N); 9.07 and 11.21 (1H, d, ^3J = 13, NH)

TABLE 2 (continued)

1	2	3
29g	1656; 3100	**DMSO-d_6**. 2.51 (3H, s, CH_3); 2.94 (2H, m, CH_2); 3.47 (2H, m, CH_2); 7.43-8.14 (8H, m, C_6H_4, C_5H_4N, =CH–); 8.54 (1H, m, ^3J = 5, C_5H_4N); 9.27 (1H, d, ^3J = 13, NH)
29h	1656; 3200-2800	**DMSO-d_6**. 2.50 (3H, s, CH_3); 2.98 (2H, t, ^3J = 7, CH_2); 3.46 (2H, t, ^3J = 7, CH_2); 7.31-8.20 (8H, m, C_6H_4, C_5H_4N, =CH–); 8.51 (1H, m, ^3J = 5, C_5H_4N); 9.56 and 11.43 (1H, d, ^3J = 13, NH)
30a	3000-2750	**DMSO-d_6**. 1.35 (3H, s, CH_3); 2.75 (2H, m, CH_2); 3.68 (2H, m, CH_2); 6.87-8.02 (12H, m, $2C_6H_4$, C_5H_4N, =CH–); 8.72 (1H, m, ^3J = 5, C_5H_4N); 12.62 (1H, d, ^3J = 10, NH); 12.80 (1H, br. s, NH)
30b	3000-2800	**DMSO-d_6**. 1.45 (3H, s, CH_3); 2.95 (2H, m, CH_2); 3.22 (2H, m, CH_2); 7.44-8.21 (11H, m, $2C_6H_4$, C_5H_4N); 8.60 (1H, m, ^3J = 5, C_5H_4N); 9.15 (1H, br. s, =CH–); 11.30 (1H, br. s, NH); 12.25 (1H, br. s, NH)
30i	1634; 3000-2750	**$CDCl_3$**. 1.45 (3H, s, CH_3); 2.56 (2H, t, ^3J = 7, CH_2); 3.27 (2H, t, ^3J = 7, CH_2); 6.78-7.35 (9H, m, $2C_6H_5$, C_5H_4N); 7.87 (4H, m, C_6H_5, C_5H_4N); 8.46 (1H, dt, ^3J = 4.9, ^4J = 1.4, C_5H_4N); 8.97 (1H, d, ^3J = 14.3, =CH–); 11.62 (1H, d, ^3J = 14.3, NH); 11.75 (1H, br. s, NH)
30j	1632; 3000-2750	**$CDCl_3$**. 1.49 (3H, s, CH_3); 2.54 (2H, m, CH_2); 3.22 (2H, m, CH_2); 3.48 (3H, s, CH_3); 3.76 (3H, s, CH_3); 6.61 (2H, m, ^3J = 9, C_6H_4); 6.80 (2H, m, ^3J = 9, C_6H_4); 7.26 (4H, m, C_6H_4, C_5H_4N); 7.84 (4H, m, C_6H_4, C_5H_4N); 8.45 (1H, m, ^3J = 5, C_5H_4N); 8.81 (1H, d, ^3J = 16, =CH–); 11.50 (1H, br. s, NH); 11.53 (1H, d, ^3J = 16, NH)

Compounds **31** can exist in the tautomeric forms **31A-C**. The ^{1}H NMR spectroscopic data conclusively points to the absence of the **31B** form due to the presence of NH proton signals in them. The predominance of form **31A** is confirmed only for compound **31a** since its spectrum shows proton signals for the fragment =CH–NH– with a characteristic spin-spin coupling of $^3J_{CHNH}$ = 9.5 Hz.

In the spectra of the remaining compounds **31b,i-l** the proton signals for the =CH– and NH groups are broad singlets and this can be a result of both tautomeric conversions of **31A** $\rightleftarrows$ **31C** and of hindered rotation around the $C_{(5')}$–N bond (**31A**). Exchange of the 4-carbonyl group (compound **29**) for arylimino (compound **31**) is accompanied by a marked low field shift of the 3-methyl group proton signal ($\Delta\delta > 1$ ppm) due to the anisotropic effect of the aromatic substituent.

EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 instrument for suspensions in vaseline oil (1800-1500 cm^{-1} region) or in hexachlorobutadiene (3600-2000 cm^{-1} region). The C–H bond stretching vibrations in the region 3050-2800 cm^{-1} are not listed. ^{1}H NMR spectra were recorded on Bruker WH-90/DS (90 MHz) and Varian Mercury BB (200 MHz) instruments using $CDCl_3$ and DMSO-d_6 with TMS as internal standard.

The characteristics of the compounds synthesized are given in Table 1 and IR and ^{1}H NMR spectroscopic data in Table 2.

The amidines and hydrazines used in this work were obtained from Acros and Maybridge.

1-(2,4-Difluorophenyl)-3-methyl-4-oxo-4,5,6,7-tetrahydroindazole (2). A refluxing mixture of 2,4-difluorophenylhydrazine hydrochloride (2.88 g, 16 mmol) in water (15 ml) and KOH (0.9 g) in ethanol (15 ml) was added to a hot solution of 2-acetyl-1,3-cyclohexanedione (2.46 g, 16 mmol) in ethanol (15 ml). The reaction product was refluxed for 30 min, conc. HCl (0.5 ml) was added, and the refluxing was continued for a further 2 h. Without cooling, the product was treated with water (50 ml) and held for 1 day in the fridge. The precipitated product **2** was filtered off and recrystallized from 50% ethanol.

1-[3,5-Di(trifluoromethyl)phenyl]- (3) and 4-Chloro-1-(2,4-difluorophenyl)-5-formyl-3-methyl-6,7-dihydroindazole (4). A solution of phosphorus oxychloride (1.1 ml, 12.0 mmol) in DMF (4 ml) was added with stirring to a solution of 4-oxo-4,5,6,7-tetrahydroindazole **1** or **2** (4 mmol) in DMF (4 ml). The mixture was held for 1 h on a boiling water bath, cooled, poured into ice, and the precipitated compound **3** or **4** was filtered off and recrystallized from ethanol.

3-[3,5-Di(trifluoromethyl)phenyl]- (5) and 8-Amino-3-(2,4-difluorophenyl)-1-methyl-4,5-dihydropyrazolo[5,4-*h*]quinazoline (10). The chloro aldehyde **3** or **4** (20 mmol) and guanidine carbonate (2.5 mmol) in a solution of sodium ethylate prepared from sodium (10 mmol) in absolute ethanol (15 ml) was refluxed for 10 h. The reaction mixture was cooled, diluted with water (20 ml), and the precipitated compound **5** or **10** was recrystallized from ethanol.

3-[3,5-Di(trifluoromethyl)phenyl]-8-(4-pyridyl)- (6), 3-[3,5-Di(trifluoromethyl)phenyl]-8-(4-trifluoromethyl-2-pyridyl)- (7), 3-(2,4-Difluorophenyl)-8-phenyl- (11), and 3-(2,4-Difluorophenyl)-1-methyl-8-(4-pyridyl)-4,5-dihydropyrazolo[5,4-*h*]quinazoline (12). The chloro aldehyde **3** or **4** (2 mmol) were refluxed for 11 h with an equimolar amount of the appropriate amidine hydrochloride in a solution of sodium ethylate prepared from sodium (4 mmol) in absolute ethanol (30 ml). The reaction mixture was cooled, diluted with water (50 ml), and the precipitated compound **11** or **12** was filtered off and recrystallized from ethanol (or from DMF in the case of the pyrimidine **7**).

3-[3,5-Di(trifluoromethyl)phenyl]-8-(1-pyrrolidyl)- (8), 3-[3,5-Di(trifluoromethyl)phenyl]-8-(4-morpholinyl)- (9), and 3-(2,4-Difluorophenyl)-1-methyl-8-(1-pyrrolidyl)-4,5-dihydropyrazolo[5,4-*h*]-quinazoline (13). The corresponding amidine hydrobromide (2 mmol) and a solution of the chloro aldehyde **3** or **4** (2 mmol) in absolute ethanol was added to a suspension of finely pulverized KOH (4 mmol) in absolute ethanol (10 ml). The mixture was refluxed for 11 h, cooled, diluted with water (100 ml), and held for 1 day in the fridge. The oily material which had solidified in this way was recrystallized from a mixture of DMF and water (1:1).

3-[3,5-Di(trifluoromethyl)phenyl]- (14) and 3-(2,4-Difluorophenyl)-1-methyl-4,5-dihydro-7H-benzo[*b*]indazolo[4,5-*e*][1,4]diazepine (15) Hydrochlorides. Separately prepared (and brought to reflux) solutions of the aldehyde **3** or **4** (2 mmol) in absolute ethanol (10 ml) and *o*-phenylenediamine (2 mmol) in absolute ethanol (10 ml) were mixed, refluxed for 5 min, and conc. HCl (0.8 ml) was added without cooling. The reaction product was held for 1 day in the fridge and the black crystalline hydrochlorides **14** and **15** were filtered off and washed on the filter with a small amount of hot absolute ethanol and then ether.

6-[3,5-Di(trifluoromethyl)phenyl]- (16) and 6-(2,4-Difluorophenyl)-8-methyl-4,5-dihydro-1H-pyrazolo[3,4-*e*]indazole (17). The chloro aldehyde **3** or **4** (2 mmol), hydrazine hydrochloride (4 mmol), and potassium carbonate (8 mmol) in absolute ethanol (20 ml) were refluxed for 3 h. After cooling, water (50 ml) was added and after 1 day compound **16** or **17** was filtered off and recrystallized from 70% ethanol.

1-[3,5-Di(trifluoromethyl)phenyl]- (18) and 4-Chloro-1-(2,4-difluorophenyl)-5-hydroxyimino-methyl-3-methyl-6,7-dihydroindazole (20). The chloro aldehyde **3** or **4** (2 mmol) and an equimolar amount of hydroxylamine hydrochloride in pyridine (6 ml) were refluxed for 3 h. After cooling, the mixture was treated with water (50 ml) and the precipitate was filtered off and recrystallized from ethanol.

1-[3,5-Di(trifluoromethyl)phenyl]- (19) and 4-Chloro-1-(2,4-difluorophenyl)-5-[3,5-di(trifluoro-methyl)phenylhydrazonomethyl]-3-methyl-6,7-dihydroindazole (21). Separately prepared solutions of the aldehyde **3** or **4** (1 mmol) in absolute ethanol (5 ml) and 3,5-ditrifluoromethylphenylhydrazine (1 mmol) in absolute ethanol (5 ml) were heated to reflux, mixed together, and refluxed for 15 min. The hydrazones **19** and **21** which precipitated on cooling were recrystallized from ethanol.

5-Carbethoxyhydrazonomethyl-4-chloro-1-(2,4-difluorophenyl)-3-methyl-6,7-dihydroindazole (22). Solutions of the aldehyde **4** (0.31 g, 1.1 mmol) in ethanol (10 ml) and carbethoxyhydrazine (0.10 g, 1.1 mmol) in ethanol (5 ml) were brought to reflux and mixed. A catalytic amount of *p*-touenesulfonic acid was added and the mixture obtained was refluxed for 1-2 min. Water (40 ml) was added without cooling and the product was held for 1 day in the fridge. The precipitated hydrazone **22** was filtered off and recrystallized from 50% ethanol.

1-[3,5-Di(trifluoromethyl)phenyl]- (23) and 5-(2-Carbethoxy-2-cyanoethenyl)-4-chloro-1-(2,4-difluorophenyl)-3-methyl-6,7-dihydroindazole (24). A mixture of the chloro aldehyde **3** or **4** (2.0 mmol), diethylamine (2 mmol), and ethyl cyanoacetate (2 mmol) was stirred for 2 h at 20°C, held for 1 day in the fridge, and the precipitated compound **23** or **24** was filtered off and recrystallized from ethanol.

1-[3,5-Di(trifluoromethyl)phenyl]- (25) and 4-Acetoxy-1-(2,4-difluorophenyl)-5-formyl-3-methyl-6,7-dihydroindazole (26). The chloro aldehyde **3** or **4** (2 mmol) in acetic anhydride (10 ml) was refluxed for 3 h and the reaction mixture was cooled and poured into crushed ice. After 1 day compound **25** or **26** was filtered off and recrystallized from 90% ethanol.

5-(2-Chlorophenylaminomethylene)- (29a), 5-(3-Trifluoromethylphenylaminomethylene)- (29b), 5-(2-Hydroxycarbonylphenylaminomethylene- (29c), 5-(2-Carbomethoxyphenylaminomethylene- (29d), 5-(2,4,6-Tribromophenylaminomethylene)- (29e), 5-(3,4,5-Trichlorophenylaminomethylene)- (29f), 5-(3-Nitrophenylaminomethylene)- (29g)-, and 5-(4-Nitrophenylaminomethylene)-3-methyl-4-oxo-1-(2-pyridyl)-4,5,6,7-tetrahydroindazole (29h). Separately prepared solutions of the indazole **27** (2 mmol) in absolute ethanol (10 ml) and the corresponding amine (2 mmol) in absolute ethanol (20 ml) were taken to reflux. The hot solutions were combined and refluxed for 2 h. The precipitation of the compound **29** began even at reflux. The reaction mixture was held for 1 day at room temperature, filtered off, and crystallized from absolute ethanol.

5-(2-Chlorophenylaminomethylene)-4-(2-chlorophenylimino)- (30a), 5-(3-Trifluoromethylphenylaminomethylene)-4-(3-trifluoromethylphenylimino)- (30b), 5-Phenylaminomethylene-4-phenylimino- (30i), 5-(4-Methoxyphenylaminomethylene)-4-(4-methoxyphenylimino)- (30j), 5-(4-Methylphenylaminomethylene)-4-(4-methylphenylimino)- (30k), and 5-(4-Bromophenylaminomethylene)-4-(4-bromophenylimino)-3-methyl-1-(2-pyridyl)-4,5,6,7-tetrahydroindazole (30l) Hydrochlorides. Separately prepared solutions of the indazole **27** (2 mmol) in absolute ethanol (10 ml) and the corresponding amine (4 mmol) in absolute ethanol (30 ml) were taken to reflux, combined, and refluxed for 2 h. The precipitation of the compound **30** began even at reflux. The reaction mixture was held for 1 day at room temperature and the precipitated **30** hydrochloride was filtered off. Compounds **30b,i** were recrystallized from absolute ethanol and compounds **30c-h,j-l** were carefully washed with absolute ethanol.

5-(2-Chlorophenylaminomethylene)-4-(2-chlorophenylimino)- (31a), 5-(3-Trifluoromethylphenylaminomethylene)-4-(3-trifluoromethylphenylimino)- (31b), 5-Phenylaminomethylene-4-phenylimino- (31i), 5-(4-Methoxyphenylaminomethylene)-4-(4-methoxyphenylimino)- (31j), 5-(4-Methylphenylaminomethylene)-4-(4-methylphenylimino)- (31k), and 5-(4-Bromophenylaminomethylene)-4-(4-bromophenylimino)-3-methyl-1-(2-pyridyl)-4,5,6,7-tetrahydroindazole (31l). A solution of $NaHCO_3$ (10% aqueous) was added dropwise with stirring to a suspension of the hydrochloride **30** (2 mmol) in ethanol (10 ml) to pH 8-9. The precipitated base **31** was filtered off and recrystallized from absolute ethanol.

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