Chemistry of Heterocyclic Compounds, Vol. 40, No. 11, 2004

NEW DERIVATIVES OF 3-AMINOINDOLE. SYNTHESIS OF 2-ARYL(HETARYL)-3-(3,5-DIMETHYL-1-PYRAZOLYL)INDOLES

N. M. Przheval'skii, N. S. Skvortsova, and I. V. Magedov

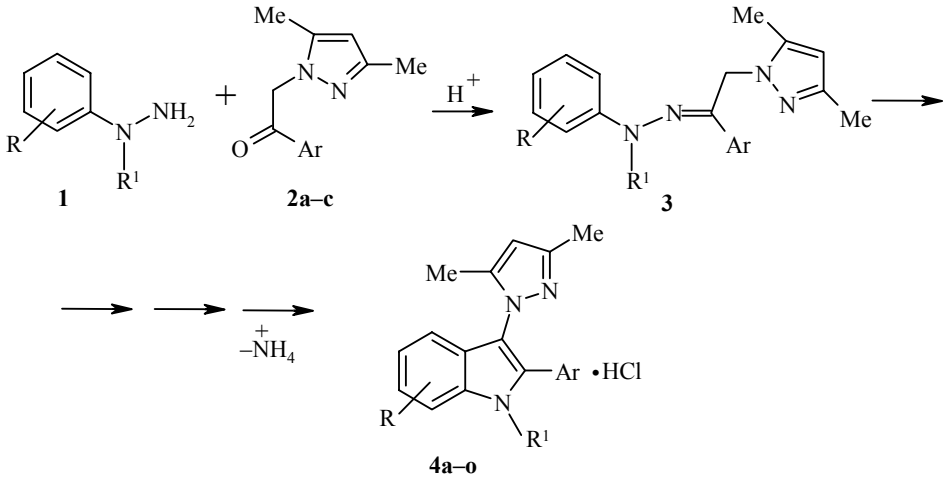
The interaction of arylhydrazines with ω-(3,5-dimethyl-1-pyrazolyl)acetophenones and acetyl(2-thiophene) leads to arylhydrazones, which are converted by Fischer cyclization into 2-aryl(thienyl)-3-(3,3-dimethyl-1-pyrazolyl)indoles with substituents in positions 1, 5, and 7.

Keywords: arylhydrazines, arylhydrazones, pyrazolylindoles.

In a continuation of investigations on the synthesis of 3-aminoindole derivatives [1, 2] we have developed a method for obtaining new systems containing pyrazole nucleus in position 3 (for a preliminary communication see [3]). These compounds are promising from the point of view of biological activity, since indoles and pyrazoles are widely known in this field [4].

Boiling a mixture of a small excess of arylhydrazines **1** with ketones **2** in ethanol in the presence of catalytic quantities of AcOH leads to arylhydrazones **3**, which were converted without isolation into indoles **4** by heating in ethanol with three moles of thionyl chloride (Fischer indolization).

Ketones **2** were synthesized by the alkylation of 3,5-dimethylpyrazole with ω-haloacetophenones and ω-chloro-2-acetylthiophene by the procedure of [5] (Table 1).



2a, **4a-d** Ar = Ph, **2b**, **4e-i** Ar = *p*-chlorophenyl, **2c**, **4j-o** Ar = 2-thienyl; **4 a**,**e**,**j** R = H, **b**,**f**,**k** R = 5-Me, **c**,**h**,**l** R = Cl, **d**,**m** R = 5-F, **g** R = 5-Br, **i**,**n** R = 5-OMe, **o** R = 7-Me, **a-h**, **j-o** R^1 = H, **i** $R^1 = CH_2Ph$

Moscow K. A. Timiryazev Agricultural Academy, Moscow 127550, Russia; e-mail: ibs@ibisc.msk.ru.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1662-1669, November, 2004. Original article submitted July 5, 2002; revision submitted October 10, 2002.

TABLE 1. Physicochemical and Spectral Characteristics of Compounds **2a-c**

Compound*	Empirical formula	Found, % / Calculated, %			mp, °C (*i*-PrOH)	^{1}H NMR spectrum, δ, ppm (*J*, Hz)			Yield, %
		C	H	N		Ar	Pyrazole ring	CH_2 (2H, s)	
2a	$C_{13}H_{14}N_2O\cdot HBr$	52.50 / 52.90	5.07 / 5.12	9.41 / 9.49	162-163	8.05 (2H, d, *J* = 8.3, H-2,6); 7.72 (1H, t, *J* = 7.2, *J* = 1.3, H-4); 7.59 (2H, t, *J* = 8.3, *J* = 7.2, H-3,5)	6.01 (1H, s, H-4); 2.33 (3H, s, CH_3-3); 2.15 (3H, s, CH_3-5)	5.76	61
2b	$C_{13}H_{13}ClN_2O\cdot HBr$	47.42 / 47.37	4.31 / 4.28	8.29 / 8.50	193-194	8.18 (2H, d, *J* = 8.8, H-2,6); 7.72 (2H, d, *J* = 8.8, H-3,5)	6.28 (1H, s, H-4); 2.35 (3H, s, CH_3-3); 2.31 (3H, s, CH_3-5)	6.13	60
2c	$C_{11}H_{12}N_2OS\cdot HBr$	43.92 / 43.86	4.33 / 4.35	9.18 / 9.30	212-213	8.25 (1H, d, *J* = 3.8, H-3); 8.21 (1H, d, *J* = 4.9, H-5); 7.38 (1H, m, H-4)	6.27 (1H, s, H-4); 2.37 (3H, s, CH_3-3); 2.31 (3H, s, CH_3-5)	6.04	54

* (3,5-Dimethyl-1H-1-pyrazolyl)methyl phenyl ketone hydrobromide (**2a**), (3,5-dimethyl-1H-1-pyrazolyl)methyl 4-chlorophenyl ketone hydrobromide (**2b**), (3,5-dimethyl-1H-1-pyrazolyl)methyl 2-thienyl ketone hydrobromide (**2c**).

TABLE 2. ^{1}H NMR Spectral Characteristics of Compounds **4a-o**

Com-pound	Chemical shifts, δ, ppm. (*J*, Hz)*				
	Indole ring	Ar	R^1	R	Pyrazole ring
1	2	3	4	5	6
4a	7.51 (1H, s, H-7); 7.23 (1H, m, H-6); 7.16 (1H, m, H-4); 7.08 (1H, m, H-5)	7.40-7.30 (5H, m, H_{arom})	11.91 (1H, br. s)	—	6.18 (1H, s, H-4); 2.26 (3H, s, CH_3-3); 1.86 (3H, s, CH_3-5)
4b	7.44 (1H, m, H-7); 7.07 (1H, d, *J* = 8.3, H-6); 7.00 (1H, s, H-4)	7.42-7.39 (5H, m, H_{arom})	11.80 (1H, br. s)	2.28 (3H, s, CH_3)	6.14 (1H, s, H-4); 2.38 (3H, s, CH_3-3); 1.91 (3H, s, CH_3-5)
4c	7.68 (1H, d, *J* = 8.3, H-7); 7.28 (1H, s, H-4); 7.26 (1H, d, *J* = 8.3, H-6)	7.49-7.40 (5H, m, H_{arom})	12.68 (1H, br. s)	—	6.31 (1H, s, H-4); 2.36 (3H, s, CH_3-3); 1.96 (3H, s, CH_3-5)
4d	7.44 (1H, m, H-7); 7.00 (1H, td, J_{H-H} = 8.3, J_{H-F} = 9.4, H-6); 6.88 (1H, dd, J_{H-F} = 9.4, H-4)	7.32 (2H, d, *J* = 8.7, H-2,6); 7.20 (3H, m, H-3,4,5)	10.17 (1H, br. s)	—	6.07 (1H, s, H-4); 2.25 (3H, s, CH_3-3); 1.87 (3H, s, CH_3-5)
4e	7.61 (1H, d, *J* = 7.7, H-4); 7.28 (1H, m, H-5); 7.26 (1H, d, *J* = 7.7, H-7); 7.14 (1H, t, *J* = 7.7, H-6)	7.49 (2H, d, *J* = 8.8, H-2,6); 7.46 (2H, d, *J* = 8.8, H-3,5)	12.35 (1H, br. s)	—	6.29 (1H, s, H-4); 2.33 (3H, s, CH_3-3); 1.98 (3H, s, CH_3-5)
4f	7.47 (1H, m, H-7); 7.03 (1H, d, *J* = 8.2, H-6); 6.10 (1H, s, H-4)	7.47 (2H, m, H-2,6); 7.41 (2H, d, *J* = 8.8, H-3,5)	12.00 (1H, br. s)	2.38 (3H, s, CH_3)	6.22 (1H, s, H-4); 2.31 (3H, s, CH_3-3); 1.95 (3H, s, CH_3-5)
4g	7.47 (1H, d, *J* = 8.8, H-7); 7.34 (1H, d, *J* = 8.8, H-6); 7.24 (1H, s, H-4)	7.48 (2H, d, *J* = 8.8, H-2,6); 7.26 (2H, d, *J* = 8.8, H-3,5)	12.10 (1H, br. s)	—	6.10 (1H, s, H-4); 2.23 (3H, s, CH_3-3); 1.83 (3H, s, CH_3-5)
4h	7.57 (1H, d, *J* = 8.8, H-7); 7.23 (1H, d, *J* = 8.8, H-6); 7.10 (1H, s, H-4)	7.48 (2H, d, *J* = 8.8, H-2,6); 7.27 (2H, d, *J* = 8.8, H-3,5)	12.08 (1H, br. s)	—	6.10 (1H, s, H-4); 2.23 (3H, s, CH_3-3); 1.83 (3H, s, CH_3-5)

TABLE 2 (continued)

1	2	3	4	5	6
4i	7.43 (1H, d, *J* = 8.3, H-7); 6.86 (1H, m, H-6); 6.60 (1H, s, H-4)	7.43 (2H, d, *J* = 8.8, H-2,6); 7.27 (2H, d, *J* = 8.8, H-3,5)	7.25-7.21 (3H, m, H-3,4,5); 6.90 (2H, m, H-2,6); 5.45 (2H, s, CH_2)	3.70 (3H, s, OCH_3)	5.93 (1H, s, H-4); 2.16 (3H, s, CH_3-3); 1.79 (3H, s, CH_3-5)
4j	7.26 (1H, m, H-7); 7.12-7.00 (3H, m, H-4,5,6)	7.05 (1H, d, *J* = 4.4, H-5); 6.63 (1H, d, *J* = 3.3, H-3); 6.55 (1H, m, H-4)	10.09 (1H, br. s)	—	6.10 (1H, s, H-4); 2.32 (3H, s, CH_3-3); 2.04 (3H, s, CH_3-5)
4k	7.35 (1H, m, H-7); 7.02 (1H, d, *J* = 8.3, H-6); 6.85 (1H, s, H-4)	7.53 (1H, d, *J* = 4.9, H-5); 7.32 (1H, m, H-3); 7.10 (1H, t, *J* = 4.9, *J* = 3.9, H-4)	11.79 (1H, br. s)	2.33 (3H, s, CH_3)	6.14 (1H, s, H-4); 2.22 (3H, s, CH_3-3); 1.90 (3H, s, CH_3-5)
4l	7.48 (1H, d, *J* = 8.3, H-7); 7.21 (1H, d, *J* = 8.3, H-6); 7.04 (1H, s, H-4)	7.59 (1H, d, *J* = 3.9, H-5); 7.38 (1H, d, *J* = 3.3, H-3); 7.13 (1H, t, *J* = 3.9, *J* = 3.3, H-4)	12.23 (1H, br. s)	—	6.17 (1H, s, H-4); 2.23 (3H, s, CH_3-3); 1.91 (3H, s, CH_3-5)
4m	7.56 (1H, m, H-7); 7.00 (1H, td, J_{H-H} = 8.3, J_{H-F} = 9.4, H-6); 6.88 (1H, d. d, J_{H-F} = 9.4, H-4)	7.64 (1H, d, *J* = 4.9, H-5); 7.54 (1H, d, *J* = 3.9, H-3); 7.16 (1H, t, *J* = 4.9, *J* = 3.9, H-4)	12.40 (1H, br. s)	—	6.26 (1H, s, H-4); 2.30 (3H, s, CH_3-3); 2.02 (3H, s, CH_3-5)
4n	7.42 (1H, m, H-7); 6.88 (1H, d, *J* = 8.8, H-6); 6.85 (1H, s, H-4)	7.57 (1H, d, *J* = 4.9, H-5); 7.39 (1H, d, *J* = 3.9, H-3); 7.13 (1H, t, *J* = 4.9, *J* = 3.9, H-4)	11.90 (1H, br. s)	3.77 (3H, s, OCH_3)	6.19 (1H, s, H-4); 2.27 (3H, s, 3-CH_3); 2.00 (3H, s, CH_3-5)
4o	7.10-7.04 (3H, m, H-4,5,6)	7.76 (1H, d, *J* = 3.9, H-3); 7.61 (1H, d, *J* = 4.9, H-5); 7.16 (1H, t, *J* = 4.9, *J* = 3.9, H-4)	11.85 (1H, br. s)	2.63 (3H, s, CH_3)	6.33 (1H, s, H-4); 2.34 (3H, s, CH_3-3); 2.03 (3H, s, CH_3-5)

* The ^{1}H NMR spectra were taken in DMSO (compounds **4a,g-i,k,l**), DMF (compounds **4b,s,e,f,m-o**), CD_3CN (compound **4d**), and $CDCl_3$ (compound **4j**).

TABLE 3. Characteristics of Indoles **4**

Compound*	Empirical formula	Name	Found, % / Calculated, %			mp, °C	Yield, %
			C	H	N		
4a	$C_{19}H_{17}N_3 \cdot HCl$	3-(3,5-Dimethyl-1H-1-pyrazolyl)-2-phenyl-1H-indole hydrochloride	70.54 / 70.47	5.70 / 5.60	12.72 / 12.98	189-190 (aq. EtOH)	46
4b	$C_{20}H_{19}N_3 \cdot HCl$	3-(3,5-Dimethyl-1H-1-pyrazolyl)-5-methyl-2-phenyl-1H-indole hydrochloride	71.20 / 71.10	5.90 / 5.97	12.16 / 12.44	290-291 (aq. EtOH)	48
4c	$C_{19}H_{16}ClN_3 \cdot HCl$	5-Chloro-3-(3,5-dimethyl-1H-1-pyrazolyl)-2-phenyl-1H-indole hydrochloride	63.61 / 63.70	4.74 / 4.78	11.70 / 11.73	292-293 (aq. EtOH)	38
4d	$C_{19}H_{16}FN_3$	5-Fluoro-3-(3,5-dimethyl-1H-1-pyrazolyl)-2-phenyl-1H-indole	74.86 / 74.74	5.26 / 5.28	13.48 / 13.76	242-243 (aq. EtOH)	40
4e	$C_{19}H_{16}ClN_3 \cdot HCl$	2-(4-Chlorophenyl)-3-(3,5-dimethyl-1H-1-pyrazolyl)-1H-indole hydrochloride	63.73 / 63.70	4.70 / 4.78	11.52 / 11.73	209-210 (aq. *i*-PrOH)	38
4f	$C_{20}H_{18}ClN_3 \cdot HCl$	2-(4-Chlorophenyl)-3-(3,5-dimethyl-1H-1-pyrazolyl)-5-methyl-1H-indole hydrochloride	64.39 / 64.52	5.18 / 5.14	10.96 / 11.29	310-311 (aq. EtOH)	57
4g	$C_{19}H_{15}BrClN_3 \cdot HCl$	5-Bromo-2-(4-chlorophenyl)-3-(3,5-dimethyl-1H-1-pyrazolyl)-1H-indole hydrochloride	52.27 / 52.20	3.74 / 3.69	9.55 / 9.61	307-308 (aq. *i*-PrOH)	25
4h	$C_{19}H_{15}Cl_2N_3 \cdot HCl$	5-Chloro-2-(4-chlorophenyl)-3-(3,5-dimethyl-1H-1-pyrazolyl)-1H-indole hydrochloride	58.80 / 58.11	4.07 / 4.11	10.53 / 10.70	302-303 (aq. EtOH)	40
4i	$C_{27}H_{24}ClN_3$	1-Benzyl-2-(4-chlorophenyl)-5-methoxy-3-(3,5-dimethyl-1H-1-pyrazolyl)-1H-indole	73.46 / 73.38	5.39 / 5.47	9.47 / 9.51	195-196 (aq. EtOH)	38
4j	$C_{17}H_{15}N_3S$	3-(3,5-Dimethyl-1H-1-pyrazolyl)-2-(2-thienyl)-1H-indole	69.47 / 69.60	5.11 / 5.15	14.30 / 14.32	230-231 (C_6H_6–C_6H_{14})	46
4k*	$C_{18}H_{17}N_3S$	3-(3,5-Dimethyl-1H-1-pyrazolyl)-5-methyl-2-(2-thienyl)-1H-indole	70.47 / 70.33	5.66 / 5.57	13.51 / 13.67	263-264 (aq. EtOH)	56
4l	$C_{17}H_{14}ClN_3S \cdot HCl$	5-Chloro-3-(3,5-dimethyl-1H-1-pyrazolyl)-2-(2-thienyl)-1H-indole hydrochloride	55.92 / 56.05	4.25 / 4.15	11.20 / 11.53	280-281 (aq. EtOH)	24
4m	$C_{17}H_{14}FN_3S \cdot HCl$	5-Fluoro-3-(3,5-dimethyl-1H-1-pyrazolyl)-2-(2-thienyl)-1H-indole hydrochloride	58.79 / 58.70	4.35 / 4.35	11.87 / 12.08	230-231 (aq. CH_3CN)	38
4n	$C_{18}H_{17}N_3OS \cdot HCl$	5-Methoxy-3-(3,5-dimethyl-1H-1-pyrazolyl)-2-(2-thienyl)-1H-indole hydrochloride	60.25 / 60.09	5.00 / 5.04	11.34 / 11.68	257-258 (aq. *i*-PrOH)	29
4o	$C_{18}H_{17}N_3S \cdot HCl$	3-(3,5-Dimethyl-1H-1-pyrazolyl)-7-methyl-2-(2-thienyl)-1H-indole hydrochloride	63.10 / 62.87	5.33 / 5.28	12.08 / 12.22	227-228 (aq. *i*-PrOH)	32

* Compounds **4d,i-k** are bases.

The structures of indoles **4** were demonstrated by ^{1}H NMR method (Table 2) and confirmed by data of elemental analysis (Table 3).

The influence of the substituents in the benzene ring of arylhydrazines **1** on the yield of pyrazolylindoles **4** was on the whole as described previously for 2-phenyl-3-(N-acylamino)indoles [2]. A methyl group increases the yield of indoles somewhat compared with unsubstituted phenylhydrazine (cf. **4b** and **4a**, **4f** and **4e**, **4k** and **4j**). Other substituents (Cl, Br, F, MeO) reduce the yield, which was discovered for the three groups of the studied indoles containing various aromatic groups in position 2 [cf. for example, for R = Cl and R = H: **4c** and **4a** (38 and 46%, phenyl), **4h** and **4e** (40 and 57%, *p*-chlorophenyl), **4l** and **4j** (24 and 46%, 2-thienyl)]. The indicated aromatic substituents (Ar) in ketones **2** , as might have been expected, had little effect on the yield of pyrazolylindole (**4**), **4a-d**, 38-46% (phenyl); **4e-i**, 24-57% (*p*-chlorophenyl); **4j-o**, 24-56% (2-thienyl).

The proposed scheme enables the preparation of compounds containing three of the most important pharmacophoric groups, indole, pyrazole, and thiophene, in one molecule (**4j-o**). Attempts to introduce an imidazole ring into indole position 3 proved to be unsuccessful. The reaction between ω-(1-imidazolyl)acetophenone and phenylhydrazine under various conditions (thionyl chloride in EtOH, PPA [polyphosphoric acid], or HBr in EtOH) led to complex mixtures of unidentified products.

EXPERIMENTAL

The ^{1}H NMR spectra of compounds **2** and **4** were recorded on a Bruker WM 250 (250 MHz) instrument. A check on the progress of reactions was effected by TLC on Sorbfil plates in the system CCl_4—EtOAc, 6 : 1.

Commercial arylhydrazines (from Lancaster and Aldrich) were used in the work. The sodium salt of 2-(4-methoxyphenyl)hydrazinesulfonic acid was synthesized by the procedure of [6].

ω-(3,5-Dimethyl-1-pyrazolyl)acetophenones and (3,5-Dimethyl-1-pyrazolyl)methyl 2-Thienyl Ketone (2a-c) were synthesized by the procedure given in [5] for pyrazole.

1H-1-Imidazolylmethyl Phenyl Ketone Hydrobromide was obtained by the alkylation of imidazole with ω-bromoacetophenone in alcohol at 0°C, yield 55%, mp 245-246°C (EtOH). ^{1}H NMR spectrum (DMSO), δ, ppm (*J*, MHz): 9.07 (1H, s, H-2 Imid); 8.07 (2H, d, *J* = 7.8, H-2,6 Phe); 7.78 (3H, m, H-4,5 Imid, H-4 Phe); 7.65 (2H, t, *J* = 7.8, *J* = 7.1, H-3,5 Phe). Found, %: C 49.29; H 4.00; N 10.16. $C_{11}H_{10}N_2O.HBr$. Calculated, %: C 49.46; H 4.15; N 10.49.

Hydrazones (3) (General Procedure). Glacial AcOH (several drops) or AcONa (6.3 mmol) was added to solution of phenylhydrazine base or hydrochloride **1** (3.3 mmol) respectively and ketone hydrobromide **2** (3.0 mmol) in the minimum volume of EtOH (10 ml). The mixture was boiled under reflux for 3 h. The resulting precipitate of NaCl and NaBr was removed from the solution by hot filtration. Alcohol was evaporated, the resulting oil was used without further purification to prepare indoles **4**.

Indoles 4a-m,o (General Procedure). Solution of thionyl chloride (9.0 mmol) in EtOH (5 ml) was added to solution of hydrazone **3a-m,o** (3.0 mmol) in EtOH (5 ml), and the mixture was boiled under reflux for 3-4 h. Alcohol was evaporated, the residue washed from the NH_4Cl formed with water, then either crystallized to obtain hydrochlorides of pyrazolylindoles (**4a-c,e-h,l,m,o**) or pyrazolylindoles were isolated as bases (**4d,i-k**) by column chromatography (silica gel L 100 × 250 μm, eluent CCl_4–EtOAc, 8:1).

5-Methoxy-3-(3,5-dimethyl-1H-1-pyrazolyl)-2-(2-thienyl)-1H-indole (4n). Solution of thionyl chloride (9.0 mmol) in EtOH (5 ml) was added to solution of 2-(4-methoxyphenyl)hydrazinesulfonic acid sodium salt (4.0 mmol) and ketone hydrobromide **2c** (3.0 mmol) in EtOH (10 ml) and the mixture was boiled under reflux for 16 h. Alcohol was evaporated, and the residue washed with water to remove ammonium salt formed. The residue was recrystallized from 2-PrOH.

REFERENCES

1. N. M. Przheval'skii, N. S. Skvortsova, and I. V. Magedov, *Khim. Geterotsikl. Soedin.*, 1210 (2002).
2. N. M. Przheval'skii, N. S. Skvortsova, and I. V. Magedov, *Khim. Geterotsikl. Soedin.*, 189 (2003).
3. N. M. Przheval'skii, N. S. Skvortsova, and I. V. Magedov, in: *Abstr. 9th Blue Danube Symp. Het. Chem.*, *Vysoke Tatry, Slovak Republic* (2002), p. 198.
4. A. T. Soldatenkov, N. M. Kolyadina, and I. V. Shendrik, *Principles of the Organic Chemistry of Medicinal Substances*, Khimiya, Moscow (2001).
5. T. W. J. Solomons, F. W. Fowler, and J. Calderazzo, *J. Am. Chem. Soc.*, **87**, 528 (1965).
6. J. Altschul, *Chem. Ber.*, **25**, 1842 (1892).