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FISCHER SYNTHESIS OF 1-, 5-, AND 7-SUBSTITUTED 3-(N-ACYLAMINO)-2-PHENYLINDOLES

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Arylhydrazones were obtained by the reaction of arylhydrazines with ω-(N-acylamino)acetophenones and were converted into 3-(N-acylamino)-2-phenylindoles with substituents at positions 1, 5, 6, and 7 by Fischer cyclization.

Keywords: arylhydrazines, arylhydrazones, 3-(N-acylamino)indoles.

The method that we developed for the synthesis of 3-(N-acylamino)-2-phenylindoles by the Fischer cyclization of the phenylhydrazones of ω-(N-acylamino)acetophenones **3**, obtained from arylhydrazines **1** and acylamino ketones **2**, was described earlier [1].

It is known that substituents of various electronic types located in the benzene ring or at the nitrogen atom of the arylhydrazones do not have a deciding effect on the [3,3]-sigmatropic rearrangement of the enehydrazines **A** → **B** (see the scheme) to indoles [2-5]. At the same time electron-donating groups as a rule accelerate while electron-accepting groups retard the indolization process [2, 5].

We investigated the electronic and steric effect of substituents in the benzene ring (R = MeO, Me, Cl, F, NO_2) and at the nitrogen atom (R^1 = Me, CH_2Ph, Ph) of the arylhydrazones of ω-(N-acylamino)acetophenones **3** on the yield of 2-phenyl-3-(N-acylamino)indoles **4**.

As shown earlier [1], the N-acyl substituent R^2CO in the phenylhydrazones **3** (R, R^1 = H) have a substantial effect on the yield of the indoles **4**, which varies between 16 and 83%. Therefore, while studying the influence of the substituents R and R^1 in the arylhydrazones **3** on the course of indolization, we compared the yield of the substituted N-acylaminoindole **4** with the yield of the corresponding 3-acylamino-2-phenylindole (**4**) (R = R^1 = H) unsubstituted at positions 1, 5, and 7 (Table 1), where all the indoles were obtained under identical conditions.

In the general case the introduction of substituents into the benzene ring of the arylhydrazones **3** reduces the yields of the acylaminoindoles **4**. The reduction in yield is insignificant for indoles with such substituents as R = 5-Me, 5-MeO, and 5-F. Much more noticeable is the decrease of the yield (by more than half) for the 5-chloro-substituted indole **4l**. The presence of the strong electron-withdrawing substituent R = 4-NO_2 in the arylhydrazone **3m** did not enable us to convert it into 5-nitro-3-(N-acylamino)indole.

The N-acylaminoindoles **4** formed during indolization contain bulky substituents at positions 2 and 3, and it could therefore be expected that additional steric factors would substantially affect the course of the reaction. In fact, the use of N-substituted arylhydrazones **3** (R = Me, CH_2Ph, Ph) greatly reduces the yield of the indoles **4**. The introduction of an *ortho* substituent into the phenyl ring of the arylhydrazone **3c** (R = 2-Me) has the same effect on the yield of the indole **4c**, and this agrees with data in [3, 5].

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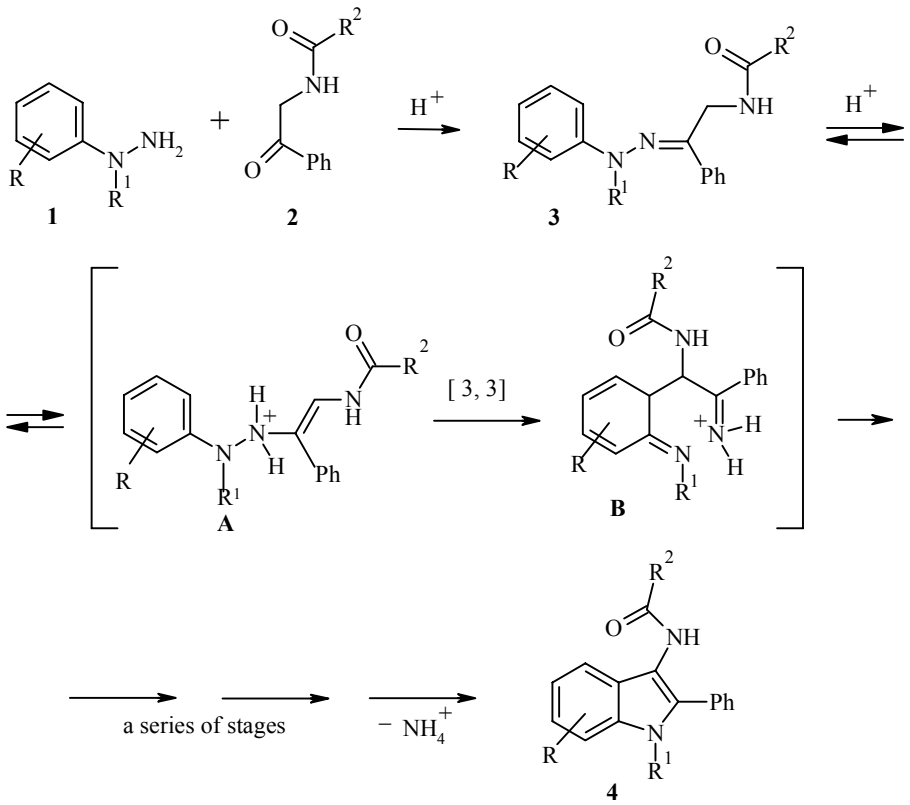

The formation of 5,6-dimethyl- and 4,5-dimethyl-3-(acylamino)indoles **4d** and **4d'** respectively is possible during the indolization of the arylhydrazone **3d** (R = 3,4-Me_2). We supposed that on account of steric factors 5,6-disubstituted **4d** and not 4,5-disubstituted 3-(N-acylamino)indole **4d'** (with four substituents in a row in the benzene ring) would be formed preferentially. However, a 1:1 mixture (according to ^{1}H NMR) of indoles **4d** and **4d'** with a smaller yield than with the unsubstituted indole was obtained as a result of the reaction.

On the whole the effect of the substituents on the formation of 3-acylaminoindoles coincides with that observed for other types of indolization [3-5].

The data obtained in the present work make it possible to consider the proposed method as a prospective method for the synthesis of derivatives of 3-aminoindoles.

EXPERIMENTAL

The ^{1}H NMR spectra of compounds **3** and **4** were recorded on a Bruker WM-250 instrument (250 MHz) in acetonitrile-d_3. the reactions were monitored by TLC on Silufol plates in the 6:1 carbon tetrachloride–ethyl acetate system.

Commercial N-(4-methylphenyl)-, N-(2-methylphenyl)-, N-(3,4-dimethylphenyl)-, N-methyl-N-phenyl-, N,N-diphenyl-, N-benzyl-N-phenyl-, N-(4-fluorophenyl)-, N-(4-chlorophenyl)-, and N-(4-nitrophenyl)hydrazines supplied by Lancaster and Aldrich were used. Sodium 2-(4-methoxyphenyl)hydrazine sulfonate was synthesized by the method in [6].

The constants and yields of the synthesized aminoindoles **4** are given in Table 1, and the ^{1}H NMR spectra are given in Table 2.

The general method for the synthesis of ω-(N-acylamino)acetophenones **2** and their constants and photochemical characteristics were given in [1].

TABLE 1. The Characteristics of the Synthesized Compounds **4**

Compound	-1H-indole	R	R^1	R^2	Empirical formula	Found, % / Calculated, %			mp, °C	Yield,* %
						C	H	N		
4a	3-(4-Chlorobenzoylamino)-5-methyl-2-phenyl-	5-Me	H	4-ClC_6H_4	$C_{22}H_{17}ClN_2O$	73.18 / 73.23	4.74 / 4.75	7.69 / 7.76	167-168	26 (33)
4b	3-(2-Bromobenzoylamino)-5-methyl-2-phenyl-	5-Me	H	2-BrC_6H_4	$C_{22}H_{17}BrN_2O$	65.42 / 65.20	4.15 / 4.23	6.62 / 6.91	200-201	41
4c	3-[(2-Chlorophenyl)-5-methyl-4-isoxazolylcarbonylamino]-7-methyl-2-phenyl-	7-Me	H	3-(2-Chlorophenyl)-5-methyl-4-isoxazolyl	$C_{26}H_{20}ClN_3O_2$	70.56 / 70.67	4.60 / 4.56	9.37 / 9.51	242-243	30 (62)
4d	3-[(2-Chlorophenyl)-5-methyl-4-isoxazolylcarbonylamino]-5,6-dimethyl-2-phenyl-	5-Me 6-Me	H	3-(2-Chlorophenyl)-5-methyl-4-isoxazolyl	$C_{27}H_{22}ClN_3O_2$	71.24 / 71.13	4.80 / 4.86	9.17 / 9.22	257-258	28 (62)
4d'	3-[(2-Chlorophenyl)-5-methyl-4-isoxazolylcarbonylamino]-4,5-dimethyl-2-phenyl-	4-Me 5-Me	H	3-(2-Chlorophenyl)-5-methyl-4-isoxazolyl						
4e	3-(4-Chlorobenzoylamino)-5-methoxy-2-phenyl-	5-OMe	H	4-ClC_6H_4	$C_{22}H_{17}ClN_2O_2$	70.24 / 70.12	4.61 / 4.55	7.43 / 7.29	140-141	32 (33)
4f	3-Benzylthioacetylamino-5-methoxy-2-phenyl-	5-OMe	H	$PhCH_2SCH_2$	$C_{24}H_{22}N_2O_2S$	71.28 / 71.62	5.36 / 5.51	7.09 / 6.96	130-131	30 (44)
4g	3-(4-Chlorobenzoylamino)-1-methyl-2-phenyl-	H	Me	4-ClC_6H_4	$C_{22}H_{17}ClN_2O$	73.04 / 73.23	4.80 / 4.75	7.72 / 7.76	180-181	22 (33)
4h	[3-(2-Chlorophenyl)-5-methyl-4-isoxazolylcarbonylamino]-1,2-diphenyl-	H	Ph	3-(2-Chlorophenyl)-5-methyl-4-isoxazolyl	$C_{31}H_{22}ClN_3O_2$	73.78 / 73.88	4.32 / 4.40	8.12 / 8.34	125-126	27 (62)
4i	1-Benzyl-3-[3-(2-chlorophenyl)-5-methylisoxazolylcarbonylamino]-2-phenyl-	H	$PhCH_2$	3-(2-Chlorophenyl)-5-methyl-4-isoxazolyl	$C_{32}H_{24}ClN_3O_2$	73.98 / 74.20	4.62 / 4.67	7.94 / 8.11	78-79	26 (62)
4j	1-Benzyl-3-(2-furoylamino)-2-phenyl-	H	$PhCH_2$	2-Furyl	$C_{26}H_{20}N_2O_2$	79.28 / 79.57	5.05 / 5.14	6.86 / 7.14	134-135	34
4k	3-Benzoylamino-5-fluoro-2-phenyl-	5-F	H	Ph	$C_{21}H_{15}FN_2O$	76.22 / 76.35	4.62 / 4.58	8.39 / 8.48	100-101	44 (52)
4l	5-Chloro-3-(2-oxo-2H-3-chromenylcarbonylamino)-2-phenyl-	5-Cl	H	3-Coumarinyl	$C_{24}H_{15}ClN_2O_3$	69.39 / 69.49	3.67 / 3.64	6.50 / 6.75	220-221	38 (83)

* The yields of the respective 3-(N-acylamino)-2-phenylindoles **4** not substituted at positions 1, 5, and 7 (R = R^1 = H) [1] are given in parentheses.

TABLE 2. The ^{1}H NMR Spectra of Compounds **4**

Com-pound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)*					
	Indole ring	2-Phenyl	R^2	R^1	R	NH, br. s.
1	2	3	4	5	6	7
4a	7.33 (1H, d, *J* = 8.8, H-7); 7.24 (1H, s, H-4); 7.04 (1H, d, *J* = 8.8, H-6)	7.72 (2H, d, *J* = 8.0, H-2, H-6); 7.44 (2H, m, H-3, H-5); 7.34 (1H, m, H-4)	7.95 (2H, d, *J* = 7.9, H-2, H-6); 7.54 (2H, d, *J* = 7.9, H-3, H-5)	8.49 (1H, s)	2.40 (3H, s, CH_3)	10.55
4b	7.43 (1H, s, H-4); 7.35 (1H, m, H-7); 7.06 (1H, d, *J* = 7.6, H-6)	7.82 (2H, d, *J* = 6.6, H-2, H-6); 7.51 (2H, m, H-3, H-5); 7.40 (1H, m, H-4)	7.72 (1H, d, *J* = 7.6, H-5); 7.64 (1H, d, *J* =7.3, H-3); 7.50-7.40 (2H, m, H-4, H-5)	8.22 (1H, s)	2.45 (3H, s, CH_3)	9.55
4c	7.19 (1H, t, *J* = 7.3, H-5); 6.99 (2H, d, *J* = 7.3, H-4, H-6)	7.65-7.46 (9H, m, C_6H_5, H-3, H-4, H-5, H-6)		9.50 (1H, s)	2.70 (3H, s, CH_3)	10.98
4d	7.14 (1H, s, H-4); 7.01 (1H, s, H-7)	2.51 (3H, s, CH_3)				
4d'	7.08 (1H, d, *J* = 8.4, H-6); 6.90 (1H, d, *J* = 8.4, H-7)	7.71-7.33 (18H, m, H arom.)		9.56 (1H, s); 9.42 (1H, s)	2.73 (3H, s, CH_3); 2.67 (3H, s, CH_3); 2.31 (6H, s, CH_3); 2.26 (3H, s, CH_3); 2.24 (3H, s, CH_3)	11.20; 11.07
4e	7.34 (1H, d, *J* = 8.2, H-7); 6.92 (1H, d, *J* = 2.2, H-4); 6.83 (1H, dd, *J* = 8.2, *J* = 2.2, H-6)	7.71 (2H, d, *J* = 8.2, H-2, H-6); 7.42 (3H, m, H-3, H-4, H-5)	7.97 (2H, d, *J* = 8.8, H-2, H-6); 7.55 (2H, d, *J* = 8.8, H-3, H-5)	8.53 (1H, s)	3.77 (3H, s, OCH_3)	9.57

TABLE 2 (continued)

1	2	3	4	5	6	7
4f	7.30 (1H, d, *J* = 2.2, H-4); 6.91 (1H, d, *J* = 8.7, H-7); 6.83 (1H, d, *J* = 8.7, H-6)	7.94 (2H, d, *J* = 8.7, H-2, H-2); 7.47 (2H, d, *J* = 8.7, H-3, H-5); 7.30 (1H, m, H-4)	8.00 (2H, d, *J* = 8.2, H-3, H-5); 7.67 (1H, m, H-4); 7.53 (2H, d, *J* = 8.2, H-2, H-6); 3.89 (2H, s, CH_2–CO); 3.30 (2H, s, CH_2–C_6H_5)	8.22 (1H, s)	3.79 (3H, s, OCH_3)	9.53
	7.53-7.45 (9H, m, H ind., H arom.)			3.71 (3H, s, CH_3)	—	8.35
4g	7.28 (1H, dd, *J* = 7.1, *J* = 8.0, H-5); 7.13 (1H, dd, *J* = 7.1, *J* = 7.7, H-6)		7.83 (2H, d, *J* = 7.6, H-2, H-6)			
4h	7.52-7.17 (18H, m, H ind., H arom.)				—	7.70
			2.62 (3H, s, CH_3)			
4i	7.40 (1H, m, H-4); 7.17 (1H, dd, *J* = 7.1, *J* = 8.0, H-6); 7.10 (1H, dd, *J* = 7.1, *J* = 7.3, H-5)	7.40-7.30 (5H, m, C_6H_5)	7.40-7.30 (4H, m, H-3, H-4, H-5, H-6); 2.57 (3H, s, CH_3)	7.19-7.20 (3H, m, H-3, H-4, H-5); 6.85 (2H, d, *J* = 7.5, H-2, H-6); 5.32 (2H, s, CH_2)	—	7.60
4j	7.50-7.35 (9H, m, H ind., H arom.)		7.09 (1H, d, *J* = 3.4, H-3); 7.06 (1H, d, *J* = 1.7, H-5); 6.58 (1H, dd, *J* = 3.4, *J* = 1.7, H-4)	7.20 (3H, m, H-3,H-4, H-5); 6.90 (2H, d, *J* = 7.8, H-2, H-6); 5.38 (2H, s, CH_2)	—	8.30
4k	7.45 (1H, m, H-7); 7.17 (1H, dd, J_{H-F} = 9.9, *J* = 2.5, H-4); 6.98 (1H, dd. d, J_{H-F} = 10.2, *J* = 9.0, *J* = 2.5, H-6)	7.74 (2H, d, *J* = 7.8, H-2, H-6); 7.60-7.50 (3H, m, H-3, H-4, H-5)	7.97 (2H, d, *J* = 7.8, H-2, H-6); 7.60 (2H, m, H-3, H-5); 7.50 (1H, m, H-4)	8.52 (1H, s)	—	9.75
4l	7.50 (1H, m, H-4); 7.43 (1H, d, *J* = 9.2, H-7); 7.18 (1H, d, *J* = 9.2, H-6)	7.76 (2H, d, *J* = 7.8, H-2, H-6); 7.48 (2H, m, H-3, H-5); 7.38 (1H, m, H-4)	8.98 (1H, s, H-4); 7.89 (1H, d, *J* = 8.3, H-8); 7.80-7.65 (3H, m, H-5, H-6, H-7)	9.84 (1H, s)	—	10.32

* The spectrum of compound **4d'** was recorded in DMSO-d_6.

General Procedure for the Production of Arylhydrazones (3). A mixture of hydrazine hydrochloride **1** (0.05 mol), acylamino ketone **2** (0.05 mol), and sodium acetate (0.05 mol) in the smallest amount of ethanol (5-10 ml) was boiled with a reflux condenser for 2 h. The precipitated sodium chloride was filtered from the hot solution. The filtrate was evaporated, and the remaining oil was crystallized (hydrazones **3a**,**c**,**d**,**k**,**m**), or recrystallized without further purification to the aminoindoles **4** (hydrazones **3b**,**e**,**f**,**h**,**i**,**j**,**l**).

ω-(4-Chlorobenzoylamino)acetophenone 4-Methylphenylhydrazone. Yield 66%; mp 86-85°C (ethanol). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 9.53 (1H, s, NH); 7.78 (2H, d, *J* = 8.4, C_6H_4–Cl-*p*, *o*- and *o*'-H); 7.58 (2H, d, *J* = 8.4, C_6H_4–Cl-*p*, *m*- and *m*'-H); 7.50 (2H, d, *J* = 6.6, N–C_6H_4–CH_3-*p*, *o*- and *o*'-H); 7.49-7.35 (5H, m, C_6H_5–C=N); 7.20 (1H, br. s, NH–C=O); 7.01 (2H, d, *J* = 8.4, N–C_6H_4–CH_3-*p*, *m*- and *m*'-H); 4.46 (2H, d, *J* = 6.2, CH_2); 2.17 (3H, s, CH_3). Found, %: C 69.86; H 5.37; N 11.26. $C_{22}H_{20}ClN_3O$. Calculated, %: C 69.93; H 5.33; N 11.12.

ω-[3-(2-Chlorophenyl)-5-methyloxazol-4-ylcarbonylamino]acetophenone 2-Methylphenylhydrazone (3c). Yield 60%; mp 90-91°C (isopropyl alcohol). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 9.51 (1H, s, NH); 7.68 (2H, d, *J* = 6.9, C_6H_5–C=N, *o*- and *o*'-H); 7.53 (1H, d, *J* = 8.3, C_6H_4–Cl-*o*, *m*-H); 7.40-7.35 (7H, m, CH arom.); 7.16 (1H, m, C_6H_4–Cl-*o*, *p*-H); 7.14 (2H, d, *J* = 8.3, C_6H_4–Cl-*o*, *o*'-H); 6.79 (1H, m, C_6H_4–Cl-*o*, *m*'-H); 6.73 (1H, br. s, NH–C=O); 4.47 (2H, d, *J* = 6.1, CH_2); 2.63 (3H, s, CH_3-isoxazole); 2.21 (3H, s, CH_3–Ph). Found, %: C 68.11; H 5.02; N 12.38. $C_{26}H_{23}ClN_4O_2$. Calculated, %: C 68.04; H 5.05; N 12.21.

ω-[3-(2-Chlorophenyl)-5-methylisoxazol-4-ylcarbonylamino]acetophenone 3,4-Dimethylphenylhydrazone (3d). Yield 70%; mp 115-116°C. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 9.54 (1H, s, NH); 7.67 (2H, d, *J* = 8.1, C_6H_5–C=N, *o*- and *o*'-H); 7.46 (1H, m, C_6H_4–Cl-*o*, *o*'-H); 7.40-7.30 (5H, m, CH arom.); 7.20 (1H, d, *J* = 8.1, C_6H_4–Cl-*o*, *m*-H); 7.00 (1H, d, *J* = 8.5, N–C_6H_3–Me_2, *m*'-H); 6.86 (1H, s, N–C_6H_3–Me_2, *o*-H); 6.84 (1H, d, *J* = 8.5, N–C_6H_3–Me_2, *o*'-H-5); 6.76 (1H, br. s, NH–C=O); 4.42 (2H, d, *J* = 6.4, CH_2); 2.64 (3H, s, CH_3-izoxazole); 2.23 (3H, s, CH_3–Ph); 2.19 (3H, s, CH_3–Ph). Found, %: C 68.65; H 5.30; N 12.01. $C_{27}H_{25}ClN_4O_2$. Calculated, %: C 68.57; H 5.33; N 11.85.

ω-(Benzoylamino)acetophenone 4-Fluorophenylhydrazone (3k). Yield 56%; mp 168-169°C (ethanol). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 10.20 (1H, s, NH); 7.91 (2H, d, *J* = 7.5, CO–C_6H_5, *o*- and *o*'-H); 7.83 (2H, d, *J* = 7.5, C_6H_5–C=N, *o*- and *o*-H); 7.74 (1H, br. s, NH–C=O); 7.55 (1H, m, CO–C_6H_5, *p*-H); 7.45-7.42 (4H, m, C_6H_5–C=N, *m*- and *m*'-H, CO–C_6H_5, *m*- and *m*'-H); 7.32 (1H, d, *J* = 6.9, C_6H_5–C=N, *p*-H); 7.21 (2H, d, *J* = 8.5, N–C_6H_4–F-*p*, *o*- and *o*'-H); 7.03 (2H, m, N–C_6H_4–F-*p*, *m*- and *m*'-H); 4.61 (2H, d, *J* = 6.3, CH_2). Found, %: C 72.28; H 5.20; N 11.96. $C_{21}H_{18}FN_3O$. Calculated, %: C 72.61; H 5.22; N 12.10.

ω-(3,4-Dimethoxyphenylacetylamino)acetophenone 4-Nitrophenylhydrazone (3m). Yield 70%; mp 168-169°C (isopropyl alcohol). ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 10.79 (1H, s, NH); 8.12 (2H, d, *J* = 8.80, N–C_6H_4–NO_2-*p*, *m*- and *m*'-H); 7.87 (2H, d, *J* = 8.25, C_6H_5–C=N, *o*- and *o*'-H); 7.40 (4H, m, C_6H_5–C=N, *m*-, *m*'- and *p*-H, NH–C=O); 7.16 (2H, d, *J* = 8.80, N–C_6H_4–NO_2-*p*, *o*- and *o*'-H); 6.78 (3H, m, CH_2–$C_6\underline{H}_3$–$(OMe)_2$); 4.42 (2H, d, *J* = 6.05, CH_2); 3.72 (3H, s, OCH_3); 3.65 (3H, s, OCH_3); 3.54 (2H, s, CO–CH_2). Found, %: C 64.72; H 5.46; N 12.40. $C_{24}H_{24}N_4O_5$. Calculated, %: C 64.28; H 5.39; N 12.49.

Production of Indoles (4). A. To a solution of the hydrazone **3** (0.03 mol) in ethanol (10 ml) we added a solution of thionyl chloride (0.09 mol) in ethanol (10 ml). The mixture was boiled with a reflux condenser for 4 h. The ammonium chloride that formed was filtered off. The alcohol was evaporated, and the residue was crystallized or the indoles **4a-d**,**g-m** were isolated by column chromatography (silica gel L 100×250 μ, eluent 6:1 carbon tetrachloride–ethyl acetate).

B. To a solution of sodium 2-(4-methoxyphenyl)hydrazine sulfonate (0.04 mol) and ω-(4-chlorobenzoylamino)acetophenone or ω-(benzylthioacetylamino)acetophenone (0.03 mol) in ethanol (10 ml) we added a solution of thionyl chloride (0.09 mol) in ethanol (10 ml). The mixture was boiled with a reflux condenser for 8 h. The precipitate was filtered off. The alcohol was distilled, and the indoles **4e**,**f** were isolated by column chromatography (the same conditions as in the production of the indoles from the hydrazones). The obtained oil was then recrystallized from isopropyl alcohol.

REFERENCES

1. N. M. Przheval'skii, N. S. Skvortsova, and I. V. Magedov, *Khim. Geterotsikl. Soedin.*, 1210 (2002).
2. N. M. Przheval'skii, L. Yu. Kostromina, and I. I. Grandberg, *Khim. Geterotsikl. Soedin.*, 867 (1988).
3. D. L. Hughes, *Org. Prep. and Proced. Int.*, **25**, 607 (1993).
4. R. J. Sundberg, Indoles, Academic Press (1996).
5. B. Robinson, *The Fischer Indole Synthesis*, Wiley, New York (1982).
6. J. Altschul, *Berichte*, **25**, 1842 (1892).