Chemistry of Heterocyclic Compounds, Vol. 40, No. 9, 2004

REACTIONS OF HYDROXYAZOLIDINES WITH π-DONOR HETEROCYCLES.

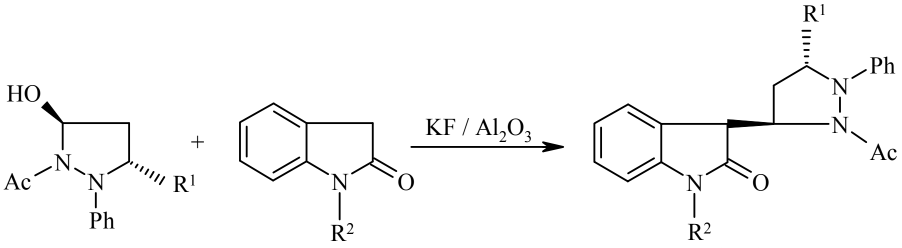
3*. REACTION OF 1-ACETYL-5-HYDROXYPYRAZOLIDINES WITH OXINDOLES

I. V. Dlinnykh[1], G. A. Golubeva[1], I. F. Leshcheva[1], V. V. Nesterov[1], M. Yu. Antipin[2], and L. A. Sviridova[1]

The reaction of oxindoles with 5-hydroxypyrazolidines on the surface of potassium fluoride-modified alumina leads to 3-(5-pyrazolidinyl)oxindoles. The structure of these products was studied.

Keywords: 5-hyroxypyrazolidine, oxindole, 3-(5-pyrazolidinyl)oxindoles, potassium fluoride on alumina.

We have developed a method for the direct introduction of the pyrazolidine substituent into the pyrazolone ring by means of the reaction of 5-hydroxypyrazolines **1** with 5-pyrazolones on the surface of a heterogeneous catalyst in a nonpolar solvent [1, 2]. In the present work, we have extended this method to oxindoles **2** and synthesized a number of previously unreported 3-(5-pyrazolidinyl)oxindoles **3a-f**. The use of potassium fluoride-modified alumina in benzene proved optimal for all the substrate pairs. The reaction is complete at 60°C after 30-60 min. Chromatographic purification of the products was required in some cases to remove dark-red oily impurities formed likely as the result of the partial oxidation of the oxindole ring during the reaction.



1a,**b** **2a**–**c** **3a**–**f**

1 a R^1 = H, **b** R^1 = Me; **2 a** R^2 = H, **b** R^2 = Me, **c** R^2 = Et; **3 a**, **c**, **e** R^1 = H, **b**, **d**, **f** R^1 = Me, **a**, **b** R^2 = H, **c**, **d** R^2 = Me, **e**, **f** R^2 = Et

---

* Communication 2, see ref. [2].

---

[1] M. V. Lomonosov Moscow State University, 119899 Moscow, Russia; e-mail: idlin@org.chem.msu.su. [2] A. N. Nesmeyanov Institute of Organoelement Compounds, 117813 Moscow, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1323-1330, September, 2004. Original article submitted March 1, 2002.

TABLE 1. Physical Characteristics of Products **3a-f**

Com-pound	Reaction time, h	Empirical formula	Found, % Calculated, % C	H	N	mp, °C	R_f	IR spectrum Solvent	ν, cm^{-1}	Yield, %
3a	0.5	$C_{19}H_{19}N_3O_2$	70.88 71.03	5.81 5.92	12.83 13.08	159-161	0.30	CCl_4	1610, 1630, 1665, 1690, 1720, 1735, 3200-3350 (bound NH), 3450 (free NH)	53
								Vaseline	1600, 1620, 1660, 1730, 3200-3300 (bound NH)	
3b	1	$C_{20}H_{21}N_3O_2$	72.03 71.64	6.42 6.27	12.29 12.54	167-169	0.35	CH_2Cl_2	1605, 1635, 1675, 1730, 3430	56
								CCl_4	3200-3350(bound NH), 3450 (free NH)	
3c	0.5	$C_{20}H_{21}N_3O_2$	71.70 71.64	6.42 6.27	12.38 12.54	146-148	0.45	Vaseline	1605, 1620, 1670, 1690, 1720	43
3d	1	$C_{21}H_{23}N_3O_2$	72.10 72.21	6.72 6.59	11.78 12.03	115-117	0.53	CH_2Cl_2	1605, 1620, 1680, 1720	63
3e	0.5	$C_{21}H_{23}N_3O_2$				127-129	0.53	CH_2Cl_2	1605, 1630, 1670, 1720	40
3f*	1	$C_{22}H_{25}N_3O_2$	72.73 72.83	6.97 6.89	11.57 11.17	110-112	0.58	CH_2Cl_2	1605, 1620, 1670, 1720	33

---

* Mass spectrum of compound **3f**, *m*/*z* (*I*, %): 349 $[M]^{+\cdot}$ (8), 306 (7), 263 (3), 203 (9), 163 (7), 162 (5), 161 (45), 146 (100), 132 (7).

The spectral data for compounds **3** given in Tables 1-3 indicate that the oxindole fragment in them exists only in the oxo form. A signal for H-3 is found in the ^{1}H NMR spectra of **3**, while their IR spectra show an oxindole carbonyl group band at 1720-1735 cm^{-1}.

The ^{1}H and ^{13}C NMR spectra of **3b** have a double set of signals. A ^{1}H NMR spectral study of these compound using the NOE technique showed that both sets of signals correspond to a pyrazolidinyloxindole having *trans* arrangement of the substituents in the pyrazolidine ring (Table 4). Thus, **3b** is probably a mixture of diastereomer racemates.

Products **3d**,**f** also have a chiral site at C-3 of the pyrazolidine ring but no double signals were found for these compounds. Although we could not obtain spectral evidence for the hydroxyindole form of these compounds, the dynamic tautomeric transition in solution probably accounts for an averaged set of signals in the spectra of **3d**,**f**. We should note that the signals of the pyrazolidine ring and its phenyl and acetyl substituents in the ^{1}H and ^{13}C NMR spectra of **3a,c,e**, which lack a substituent at C-3', are very broadened, lack clear shape, and are given as regions.

The ^{1}H NMR NOE data indicate that **3d** has *trans* arrangement of the substituents in the pyrazolidine ring (Table 2), which is analogous to pyrazolidinylpyrazolones studied in our previous work [2]. The nuclear Overhauser effect found between H-3 of the oxindole ring and H-4' of the pyrazolidine ring indicates their proximity in space.

An X-ray diffraction structural analysis established the structure of **3d** in the crystalline state (Fig. 1), while the bond lengths, bond angles, and major torsion angles are given in Tables 5-7. A benzene solvent molecule is found in a special position in the crystal of this compound obtained upon recrystallization from a mixture of ether and benzene. Thus, one-half solvent molecule is found per product molecule.

The pyrazolidine ring in **3d** has *twist* conformation: $N_{(20)}$ and $C_{(10)}$ are twisted to opposite sides of the plane of the other ring atoms by 0.140 and -0.380 Å, respectively. The methyl and acetyl groups are on the same side of the pyrazolidine ring. The dihedral angle between the planes of the oxindole and phenyl rings is 15.3°. The observed mutual arrangement of the substituents in the molecule **3d** stipulates the existence of the forced intramolecular nonvalent contacts: $C_{(1)}\cdots C_{(14)}$, 3.270(2); $C_{(12)}\cdots O_{(24)}$, 3.091(2); $C_{(19)}\cdots N_{(2)}$, 3.339(2); $C_{(19)}\cdots C_{(3)}$, 3.470; $C_{(19)}\cdots C_{(21)}$, 3.469(2) Å, which are less than the sums of the van der Waals radii of the corresponding atom pairs [3]. The following intermolecular nonbonding contacts can be suggested to be in the crystal of **3d**: $C_{(5)}\cdots C_{(21)}$, 3.451(3) (1-*x*, -*y*, 1-*z*), $C_{(10)}\cdots O_{(23)}$, 3.247(2) (-*x*, -*z*, 1-*z*), $C_{(15)}\cdots O_{(24)}$, 3.208(3) Å (-*x*, -1-*y*, -*z*) (see Fig. 1*b*).

TABLE 2. ^{1}H NMR Spectra of **3a-f**

Com-pound	Chemical shifts, δ, ppm						
	3-H	3'-H, m	4'-H, 4'-H', m	5'-H, m	CH_3CO, s	3'-CH_3, d	R^2
3a*	3.2	3.3-3.8	2.0-2.2	4.83	2.08	—	9.0 (NH)
3b	3.3, 3.4*[2]	4.2, 4.2	2.1; 2.4 1.9; 2.7	4.8, 4.8	2.0, 2.1	1.2, 1.25	9.3, 9.6 (NH)
3c	3.4-4.0	3.20-3.50	2.0-2.5	5.1	2.2	—	3.0 (CH_3)
3d	3.6	4.3	2.06, 2.83	5.15	1.98	1.27	2.68 (CH_3)
3e	3.4-4.0	3.30-3.50	2.0-2.3	4.95	2.08	—	1.17; 3.3-3.5 (C_2H_5)
3f	3.3	4.3	2.1; 2.7	5.0	2.0	1.26	1.28; 3.3 (C_2H_5)

---

* Regions of appearance are given for **3a,c,e** due to strong signal broadening.

*[2] Signals for pairs of diastereomer racemates are given.

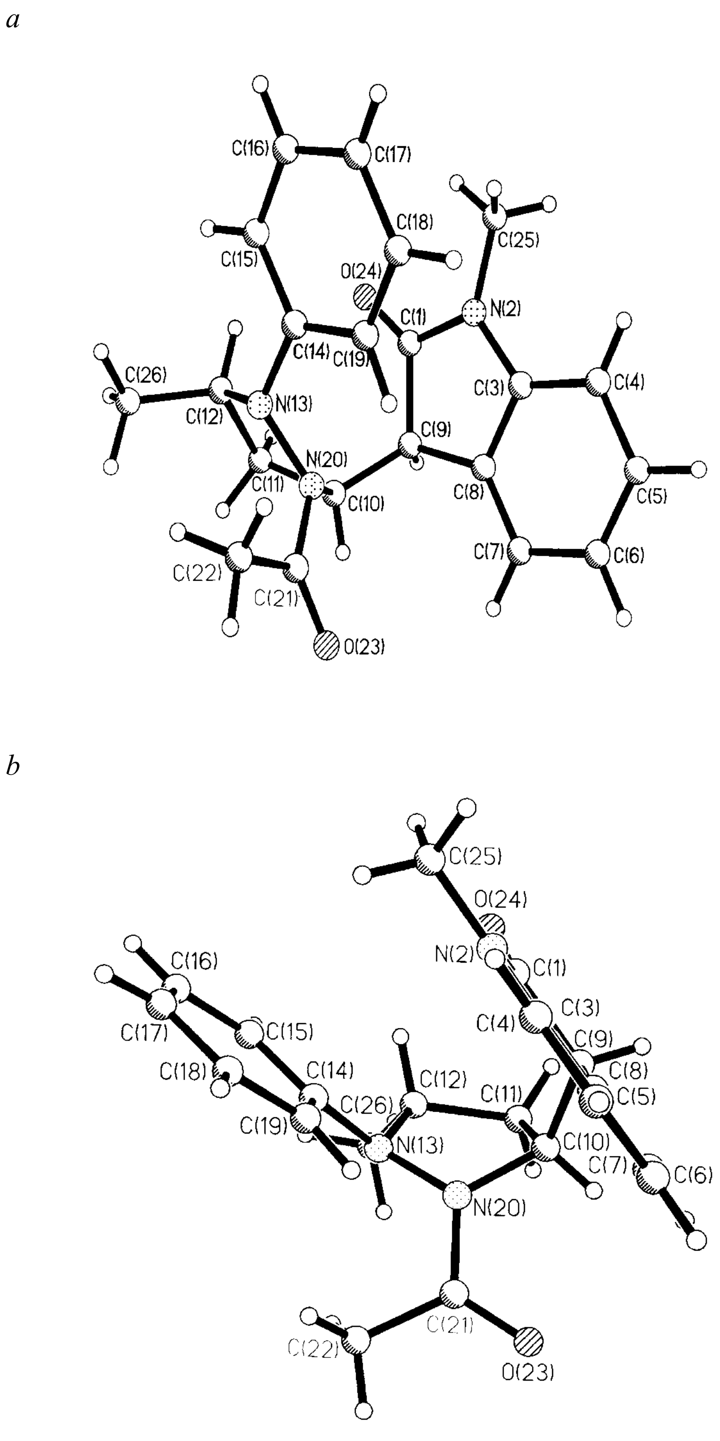


Fig. 1. General view of **3d** in two projections (*a* and *b*).

The other geometrical parameters in this molecule have ordinary values [4].

TABLE 3. ^{13}C NMR Spectra of **3a-f**

Atom	Chemical shifts, δ, ppm					
	3a	**3b***	**3c**	**3d**	**3e**	**3f**
C(2)*[2]	177.5	176.49; 177.10	174.76	174.34		174.04
C(3)	57.06	56.90; 58.60	56.48	60.0	56.94	60.23
C(3a)	128.41	128.20; 127.44	128.74	128.38	128.33	128.20
C(4)	121.95	121.64; 122.18	121.90	122.08	121.09	121.65
C(5)	124.94	124.57; 125.04	124.56	124.65	124.97	124.57
C(6)	128.26	127.00; 127.44	128.18	128.35	128.28	126.63
C(7)	110.0	109.93; 109.84	107.70	107.66	108.03	107.84
C(7a)	142.0	142.15; 141.68	144.31	144.17	143.68	143.39
C(3')*[3]	46.0-48.0	60.59; 60.11	46.0-48.0	56.73	44.0-48.0	56.87
C(4')	28.0-32.0	32.30; 36.39	30.0	37.96	27.0-29.0	38.12
C(5')	52.0-54.0	49.75; 48.23	53.0	48.39	51.0-52.0	48.88
CH_3(3')	—	20.46; 20.46	—	20.85	—	20.83
$\underline{C}H_3CO$	21.0	21.30; 21.76	21.0	21.27	20.0-21.0	20.98
$CH_3\underline{C}O$*[2]		176.98; 176.94		176.31		176.35
PhC_o	116.0	114.32; 114.16	114.0	113.07	113.0-115.0	113.84
C_p	121.0	121.10; 121.90	120.8	120.07	120.0-121.0	120.49
C_m	129.17	129.05; 128.33	128.73	128.95	129.00	128.88
C_i	150.5	150.05; 149.72	150.25	149.69	150.0-151.0	149.82
R^2		—	25.55	25.36	12.43;34.42	12.20;34.16

---

* Signals of pairs of diastereomer racemates are given.

*[2] The signal assignment may be reversed.

*[3] Regions of appearance are given for **3a,c,e** due to strong broadening of some of the signals.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer, while the ^{1}H and ^{13}C NMR spectra were taken on a VXR-400 spectrometer at 400 and 100 MHz, respectively, for chloroform solutions at 28°C with TMS as the internal standard. The NOEDIF program was used for the NOE experiments.

X-ray Diffraction Structural Analysis. The unit cell parameters for triclinic crystals of **3d** at -120°C: a = 8.808(4), b = 9.748(5), c = 13.373(6) Å; α = 109.32(4), β = 103.83(4), γ = 99.78(4)°; V = 1012(1) Å^3; d_{calc} = 1.274 g/cm^3; Z = 2; space group $P1$. The unit cell parameters and intensities of 4454 independent

TABLE 4. NOE Values for Compounds **3b**,**d***

Compound	Observed protons	η, %				
		Saturated protons*2				
		H-3'	H-4'	H'-4'	H-5'	H-3
3b	H-3'				—	—
	H-4'	3.26; 2.7*3	6.5		—	–
	H'-4'	—	9.1		3.0; 2.7	2.14
	H-3	—	8.1		3.1; 1.5	
3d	H-3'		7.6			
	H-4'	5.0		17.6	—	
	H'-4'	—	19.7		4.6	
	H-5'	—	—	9.5		
	H-3		9.0	—	9.0	

---

* For compound **3d**: $\eta_{o\text{-Ph}}$ (H-3') = 11.7; $\eta_{4'\text{-H}}$ (H-5') = 4.1.

*2 H-4' is the downfield signal, while H'-4' is the upfield signal.

*3 The η values for individual diastereomer racemates.

TABLE 5. Bond Lengths (*d*) in **3d**

Bond	*d*, Å	Bond	*d*, Å
$O_{(23)}$–$C_{(22)}$	1.224(2)	$C_{(6)}$–$C_{(7)}$	1.402(2)
$O_{(24)}$–$C_{(1)}$	1.221(2)	$C_{(7)}$–$C_{(8)}$	1.381(3)
$N_{(1)}$–$C_{(1)}$	1.371(2)	$C_{(8)}$–$C_{(9)}$	1.508(2)
$N_{(2)}$–$C_{(3)}$	1.402(2)	$C_{(9)}$–$C_{(10)}$	1.541(2)
$N_{(2)}$–$C_{(25)}$	1.445(3)	$C_{(10)}$–$C_{(11)}$	1.536(2)
$N_{(13)}$–$C_{(14)}$	1.413(2)	$C_{(11)}$–$C_{(12)}$	1.546(2)
$N_{(13)}$–$N_{(20)}$	1.423(2)	$C_{(12)}$–$C_{(26)}$	1.524(2)
$N_{(13)}$–$C_{(12)}$	1.492(2)	$C_{(14)}$–$C_{(19)}$	1.400(2)
$N_{(20)}$–$C_{(22)}$	1.375(3)	$C_{(14)}$–$C_{(15)}$	1.401(2)
$N_{(20)}$–$C_{(10)}$	1.473(2)	$C_{(15)}$–$C_{(16)}$	1.386(3)
$C_{(1)}$–$C_{(9)}$	1.530(3)	$C_{(16)}$–$C_{(17)}$	1.392(3)
$C_{(3)}$–$C_{(8)}$	1.390(3)	$C_{(17)}$–$C_{(18)}$	1.388(3)
$C_{(3)}$–$C_{(4)}$	1.393(2)	$C_{(18)}$–$C_{(19)}$	1.391(2)
$C_{(4)}$–$C_{(5)}$	1.395(3)	$C_{(21)}$–$C_{(22)}$	1.506(2)
$C_{(5)}$–$C_{(6)}$	1.383(3)		

reflections were measured on a four-circle automatic Syntex P2(1) diffractometer using γMo*K*α radiation, graphite monochromator, and θ/2θ scanning up to θ_{max} = 27°. The structure was solved by the direct method with detection of all the non-hydrogen atoms and refined by the full matrix method of least squares anisotropically for the non-hydrogen atoms. All the hydrogen atoms were objectively found in the Fourier map and refined isotropically. The final R_1 = 0.059 using 3597 reflections with $I > 2\sigma$ and R_w = 0.1706 using 4399 reflections. All the calculations were carried out using the PC version of the SHELXTL PLUS program package.

The adsorbent catalyst was prepared by a modification of the method reported by Bergbreiter and Lalonde [5]. Potassium fluoride was dissolved in a minimal amount of hot water and a 20-30-fold excess of alumina (relative to the mass of KF) was added. The suspension obtained was thoroughly stirred and left overnight. Water was distilled off in vacuum. The final traces of water were removed by repeated distillation

TABLE 6. Bond Angles (ω) in **3d**

Angle	ω, deg.	Angle	ω, deg.
$C_{(1)}-N_{(2)}-C_{(3)}$	111.3(2)	$C_{(8)}-C_{(9)}-C_{(1)}$	102.6(1)
$C_{(1)}-N_{(2)}-C_{(25)}$	123.5(2)	$C_{(8)}-C_{(9)}-C_{(10)}$	114.7(2)
$C_{(3)}-N_{(2)}-C_{(25)}$	125.1(2)	$C_{(1)}-C_{(9)}-C_{(10)}$	117.5(1)
$C_{(14)}-N_{(13)}-N_{(20)}$	116.1(1)	$N_{(20)}-C_{(10)}-C_{(11)}$	101.6(1)
$C_{(14)}-N_{(13)}-C_{(12)}$	120.3(1)	$N_{(20)}-C_{(10)}-C_{(9)}$	113.5(1)
$N_{(20)}-N_{(13)}-C_{(12)}$	107.9(1)	$C_{(11)}-C_{(10)}-C_{(9)}$	115.7(2)
$C_{(22)}-N_{(20)}-N_{(13)}$	119.1(1)	$C_{(10)}-C_{(11)}-C_{(12)}$	105.3(1)
$C_{(22)}-N_{(20)}-C_{(10)}$	120.9(1)	$N_{(13)}-C_{(12)}-C_{(26)}$	110.9(2)
$N_{(13)}-N_{(20)}-C_{(10)}$	109.2(1)	$N_{(13)}-C_{(12)}-C_{(11)}$	104.7(1)
$O_{(24)}-C_{(1)}-N_{(2)}$	124.9(2)	$C_{(26)}-C_{(12)}-C_{(11)}$	112.9(2)
$O_{(24)}-C_{(1)}-C_{(9)}$	127.3(2)	$C_{(19)}-C_{(14)}-C_{(15)}$	118.9(2)
$N_{(2)}-C_{(1)}-C_{(9)}$	107.8(2)	$C_{(19)}-C_{(14)}-N_{(13)}$	120.9(2)
$C_{(8)}-C_{(3)}-C_{(4)}$	122.2(2)	$C_{(15)}-C_{(14)}-N_{(13)}$	120.0(1)
$C_{(8)}-C_{(3)}-N_{(2)}$	109.8(2)	$C_{(16)}-C_{(15)}-C_{(14)}$	120.0(2)
$C_{(4)}-C_{(3)}-N_{(2)}$	128.0(2)	$C_{(15)}-C_{(16)}-C_{(17)}$	121.3(2)
$C_{(3)}-C_{(4)}-C_{(5)}$	116.9(2)	$C_{(18)}-C_{(17)}-C_{(16)}$	118.7(2)
$C_{(6)}-C_{(5)}-C_{(4)}$	121.6(2)	$C_{(17)}-C_{(18)}-C_{(19)}$	121.0(2)
$C_{(5)}-C_{(6)}-C_{(7)}$	120.4(2)	$C_{(18)}-C_{(19)}-C_{(14)}$	120.2(2)
$C_{(8)}-C_{(7)}-C_{(6)}$	118.7(2)	$O_{(23)}-C_{(22)}-N_{(20)}$	121.0(2)
$C_{(7)}-C_{(8)}-C_{(3)}$	120.1(2)	$O_{(23)}-C_{(22)}-C_{(21)}$	122.2(2)
$C_{(7)}-C_{(8)}-C_{9()}$	131.4(2)	$N_{(20)}-C_{(22)}-C_{(21)}$	116.7(2)
$C_{(3)}-C_{(8)}-C_{(9)}$	108.5(2)		

TABLE 7. Major Torsion Angles (τ) in **3d**

Angle	τ, deg.	Angle	τ, deg.
$C_{(12)}-N_{(13)}-N_{(20)}-C_{(10)}$	26.1(2)	$C_{(14)}-N_{(13)}-C_{(12)}-C_{(26)}$	-107.4(2)
$C_{(14)}-N_{(13)}-N_{(20)}-C_{(22)}$	103.0(2)	$C_{(10)}-C_{(11)}-C_{(12)}-N_{(13)}$	-14.9(2)
$O_{(24)}-C_{(1)}-C_{(9)}-C_{(10)}$	-56.1(2)	$C_{(10)}-C_{(11)}-C_{(12)}-C_{(26)}$	-135.6(2)
$N_{(2)}-C_{(1)}-C_{(9)}-C_{(10)}$	126.3(2)	$N_{(20)}-N_{(13)}-C_{(14)}-C_{(15)}$	165.7(1)
$C_{(22)}-N_{(20)}-C_{(10)}-C_{(9)}$	-125.7(2)	$C_{(12)}-N_{(13)}-C_{(14)}-C_{(15)}$	32.6(2)
$C_{(1)}-C_{(9)}-C_{(10)}-N_{(20)}$	-68.1(2)	$N_{(13)}-N_{(20)}-C_{(22)}-C_{(21)}$	-18.7(2)
$C_{(8)}-C_{(9)}-C_{(10)}-C_{(11)}$	169.5(1)	$C_{(10)}-N_{(20)}-C_{(22)}-C_{(21)}$	-159.1(2)

with benzene. The mass was dried for 48 h in vacuum at 80-100°C. The course of the reactions and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates with 1:1 benzene–ethyl acetate as the eluent. The plates were developed with iodine vapor and ethanolic $FeCl_3$. The products were purified on a column packed with dry silica gel L 5/40.

1-Acetyl-5-hydroxy-2-phenylpyrazolidines 1a,b were prepared according to our previous procedure [6].

Oxindoles 2a-c were prepared according to Stolle from the corresponding chloroacetanilides [7].

3-(1-Acetyl-2-phenyl-5-pyrazolidinyl)oxindoles 3a-f. A solution of oxindole **2** (5 mmol) in a minimal amount of benzene was added to adsorbent (5 g). The mixture was shaken and benzene was removed in vacuum. A solution of 4-hydroxypyrazolidine **1** (5 mmol) in benzene (30 ml) was added. The reaction mixture was stirred at 60°C. At the end of the reaction as indicated by thin-layer chromatography, the products were extracted from the solid phase with chloroform. The combined extracts were evaporated in vacuum and the dry residue was crystallized from benzene–ether (**3b**,**d**) or subjected to chromatography.

REFERENCES

1. L. A. Sviridova, G. A. Golubeva, and I. V. Dlinnykh, *Khim. Geterotsikl. Soedin.*, 1657 (1996).
2. L. A. Sviridova, G. A. Golubeva, I. V. Dlinnykh, I. F. Leshcheva, L. D. Ashkinadze, V. V. Nesterov, and M. Yu. Antipin, *Khim. Geterotsikl. Soedin.*, 1079 (1998).
3. R. S. Rowland and R. Taylor, *J. Phys. Chem.*, **100**, 7384 (1996).
4. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, No. 12, S1 (1987).
5. D. E. Bergbreiter and J. J. Lalonde, *J. Org. Chem.*, **52**, 1601 (1987).
6. A. V. Dovgilevich, K. N. Zelenin, A. A. Espenbetov, Yu. T. Struchkov, I. P. Bezhan, L. A. Sviridova, G. A. Golubeva, M. Yu. Malov, and Yu. G. Bundel', *Khim. Geterotsikl. Soedin.*, 1242 (1985).
7. G. I. Zhungietu, *Oxindole and Its Derivatives* [in Russian], Shtiintsa, Kishinev (1973), p. 45.