4. N. S. Prostakov, V. P. Shalimov, and Galo B. Montenegro Kordova, Khim. Geterosikl. Soedin., No. 11, 1525 (1984).
5. L. L. Iversen, Brit. Med. Bull., 29, 130 (1963).
6. N. S. Prostakov, V. P. Shalimov, Galo Montenegro Kordova, and N. I. Leonova, Khim.-farm. Zh., No. 11, 1333 (1984).
7. G. Hvistendahl and K. Undheim, Org. Mass Spectrom., 3, 821 (1970).
8. R. A. Khmel'nitskii, P. B. Terent'ev, A. A. Polyakova, and A. N. Kost, Dokl. Akad. Nauk SSSR, 167, 1066 (1966).
9. A. A. Polyakov and R. A. Khmel'nitskii, Mass Spectrometry in Organic Chemistry [in Russian], Leningrad (1972), p. 68.
10. A. I. Ermakov, Zh. K. Torosyan, and Yu. N. Sheinker, Khim. Geterotsikl. Soedin., No. 14, 507 (1979).
11. R. S. Gohlke and F. W. McLafferty, Anal. Chem., 34, 1281 (1962).
12. P. B. Terent'ev, Mass Spectrometry in Organic Chemistry [in Russian], Vysshch. Shkola, Moscow (1979), p. 82.
13. F. W. McLafferty and L. S. Gohlke, Anal. Chem., 31, 2076 (1959).

SYNTHESIS OF AROMATIC PYRAZOLO[4,5-b]PYRIDINE DERIVATIVES

V. D. Orlov, Kh. Kiroga, and N. N. Kolos

UDC 547.779.1'828.07:542.953.2:543.422

Cyclocondensation of chalcones with 5-amino-3-methyl-1-phenylpyrazole leads to the formation of 2,4-diaryl-5-methyl-7-phenyl-3,4-dihydropyrazolo-[4,5-b]pyridines, which undergo aromatization upon treatment with N-bromosuccinimide.

Condensation of aminopyrazoles with β-dicarbonyl compounds represents a known method for the synthesis of pyrazolo[4,5-b]pyridines [1]. Partial hydrogenation reactions of these bicyclic derivatives have not been investigated however.

Our goal in the present paper was to study the condensation of 5-amino-3-methyl-1-phenylpyrazole (I) with chalcones (IIa-k) as a method for the synthesis of dihydropyrazolopyridine derivatives. We have found that reflux of equimolar amounts of compound I and IIa-k in DMF for 1 h leads to the formation of 2,4-diaryl-5-methyl-7-phenyl-3,4-dihydropyrazolo[4,5-b]-pyridines (IIIa-k, Table 1). If the reaction mixtures are subjected to further reflux, oxidation products IVa-e, g-k are formed; these may be separated from IIIa-e, g-k by chromatography. Compounds IVa-e, g-k (Table 2) can be obtained in excellent yield by treatment of the dihydro derivatives IIIa-e, g-k with N-bromosuccinimide. Compound IIIf is an exception. It does not undergo oxidation with N-bromosuccinimide, but can be converted to the pyrazolopyridine derivative IVf via the dibromide VIf.

Especially noteworthy is the reaction of benzylideneacetone VIII with amine (I); in contrast to the reactions of chalcones, the pyrazolopyridine IVℓ was formed directly, and the intermediate dihydroderivative IIIℓ could not be isolated even under an inert atmosphere.

Independent experiments revealed (see Scheme) that pyrazolo[4,5-b]pyridine derivatives IV could also be obtained in reactions of amine I with dibenzoylmethane V in acetic acid and with α,β-dibromides VIa, f and a chalcone α-epoxide VII; the reaction conditions were the same as those used in reactions with the chalcones themselves. The highest yields are obtained in reactions of the dibromides VIa, f; this represents a very convenient method for the direct synthesis of heterocycles IV.

The formation of dihydropyrazolo[4,5-b]pyridine derivatives (IIIa-k) and their oxidation products IVa-k were confirmed by elemental analysis and spectroscopic characterization.

A. M. Gor'kii Khar'kov State University, Kharkov. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1247-1251, September, 1987. Original article submitted April 28, 1986.

0009-3122/87/2309-0997$12.50

TABLE 1. 5-Methyl-7-phenyl-2-(4-R^1-phenyl)-4-(4-R-phenyl)-3,4-dihydropyrazolo[4,5-b]pyridines

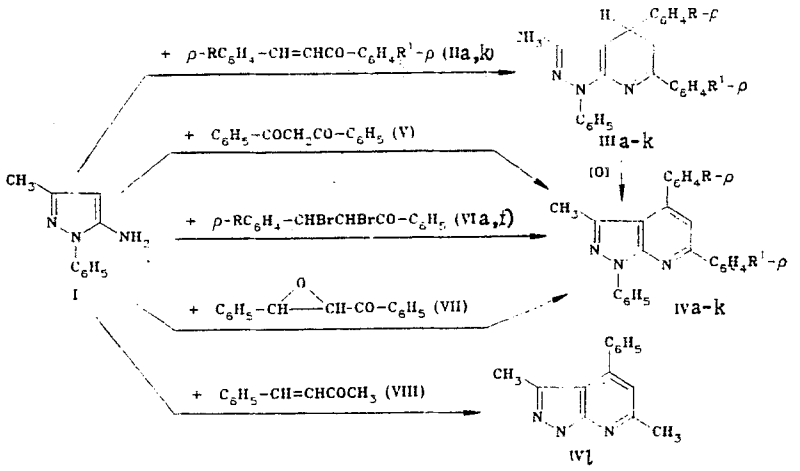
Compound	T_{mp}, °C	UV spectrum (in methanol), λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	PMR spectrum: δ_{CH_3}, s	PMR spectrum: δ_{CH_2}, t	PMR spectrum: δ_{CH}, d	PMR spectrum: J_{AX}, Hz	Found N, %	Molecular formula	Calc. N, %	Yield, %
IIIa	136—137	323 (15,9), 233 (25,9)	2,1	3,15	4,18	8,4	11,8	$C_{25}H_{21}N_3$	11,6	65
IIIb	124	323 (14,9), 231 (23,7)	2,02	3,21	4,19	8,6	11,0	$C_{25}H_{23}N_3$	11,1	60
IIIc	110—111	323 (17,9), 235 (27,6)	2,05	3,22	4,24	8,2	10,8	$C_{26}H_{23}N_3O$	10,8	50
IIId	136—137	323 (15,6), 227 (26,9)					10,7	$C_{25}H_{20}ClN_3$	10,6	45
IIIe	127—128	323 (15,2), 231 (27,7)	2,04	3,2	4,22	8,7	9,5	$C_{25}H_{20}BrN_3$	9,5	52
IIIf	173—174	325 (15,4), 276 (19,5), 234 (23,9)	2,05	3,26	4,39	8,0	13,9	$C_{25}H_{20}N_4O_2$	13,7	50
IIIg	110—112	327 (15,6), 235 (20,8)	2,02	3,22	4,34	8,1	11,0	$C_{26}H_{23}N_3$	11,1	43
IIIh	131—132	338 (23,4), 238 (19,9)	2,00	3,19	4,21	8,0	10,6	$C_{26}H_{23}N_3O$	10,7	50
IIIi	154—155	330 (15,2), 237 (21,9)	2,01	3,22	4,29	8,0	10,8	$C_{25}H_{20}ClN_3$	10,6	65
IIIj	161—162	334 (17,4), 238 (23,4)	2,05	3,22	4,25	8,6	9,5	$C_{25}H_{20}BrN_3$	9,5	62
IIIk	162—163	365 (13,6), 327 (13,2), 257 (18,7)	2,03	3,28	4,33	9,0	13,7	$C_{25}H_{20}N_4O_2$	13,7	73

*The δ values for the 5-CH_3 groups are given here; δ_{CH_3} values for the substituents in compounds IIIb, c, g, and h are: 2.39, 3.81; 2.31; and 3.82 ppm, respectively.

TABLE 2. 5-Methyl-7-phenyl-2-(4-R^1-phenyl)-4-(4-R-phenyl)-pyrazolo[4,5-b]pyridines

Compound	T_{mp}, °C	UV spectrum (in methanol), λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	Luminescence spectrum, λ_{max}, nm	Stokes' shift, cm^{-1}	Found N, %	Molecular formula	Calc. N, %	Yield, %
IVa**	130—132	334 (8,8), 306 (15,1), 270 (30,7), 247 (31,1)	446	7520	11,7	$C_{25}H_{19}N_3$	11,6	70
IVb	146—147	337 (8,8), 306 (13,7), 270 (28,5), 249 (26,1)	440	6950	11,3	$C_{26}H_{21}N_3$	11,2	65
IVc	158—160	338 (10,2), 309 (16,1), 268 (35,6), 248 (35,9)	457	7704	10,8	$C_{25}H_{18}ClN_3$	10,6	70
IVd	140—142	337 (9,6), 308 (15,3), 268 (35,1), 250 (35,7)	450	7450	9,3	$C_{25}H_{18}BrN_3$	9,5	72
IVf	202	343 (7,1), 268 (31,1), 242 (mp)	—	—	13,8	$C_{25}H_{18}N_4O_2$	13,8	
IVg	133—135	338 (mp), 312 (11,7), 268 (19,7), 249 (20,6)	442	6960	11,0	$C_{26}H_{21}N_3$	11,2	60
IVh	116—118	329 (21,4), 270 (mp), 249 (31,1)	443	7822	10,9	$C_{26}H_{21}N_3O$	10,7	66
IVi	153	338 (9,5), 309 (18,9), 270 (32,5), 249 (35,3)	443	7012	10,3	$C_{25}H_{18}ClN_3$	10,6	68
IVj	147	335 (10,8), 309 (20,5), 271 (33,6), 249 (36,7)	448	7530	9,5	$C_{25}H_{18}BrN_3$	9,5	70
IVk	184	321 (24,9), 260 (31,8)	—	—	13,8	$C_{25}H_{18}N_4O_2$	13,8	60
IVl***	154—155	321 (6,7), 260 (27,3)	—	—	14,1	$C_{20}H_{17}N_3$	14,0	60

*Yields of compounds IV obtained upon treatment of compounds III with N-bromosuccinimide.
†The $\delta_{5\text{-}CH_3}$ values and $\delta_{3\text{-}CH_3}$ values in the PMR spectra of compounds IVa, d are equal to 2.39 and 7.29; and 2.29 and 7.29 ppm, respectively.
‡CH_3 in place of R^1, C_6H_4; in the PMR spectrum: δ_{CH_3} 2.25; 2.7; δ_{CH} 6.95 ppm.



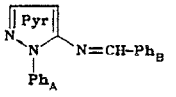
II—IV, VI a R=H, b R=CH_3, c R=OCH_3, d R=Cl, e R=Br, f R=NO_2, II—IV, VI a-f R^1=H, II—IV g-k R=H, g R^1=CH_3, h R^1=OCH_3, i R^1=Cl, j R^1=Br, k R^1=NO_2

For instance, the IR spectra of compounds III, obtained for KBr pellets, contain C=N stretching vibrational bands and quite intense bands due to acyclic C–H bonds (2870-3060 cm^{-1}). These bands disappear upon oxidation of comopunds III to IV.

The electronic absorption spectra of compounds III are characterized by the presence of two absorption bands in the 320-400 nm region. The data in Table 1 clearly show that the λ_{max} values for the long-wavelength bands are very sensitive to the effects of substituents R^1; the maximum effect was observed in the case of a nitro group substituent. These data demonstrate unequivocally that the aromatic ring containing the R^1 substituent is included in the conjugation chain, and thus that condensation of the amino group in compound I with a ketone carbonyl group takes place during the course of the reaction. Quantum mechanical calculations carried out for the π-system of a flat model of molecule IIIa were in excellent agreement with experimental results. The long-wavelength absorption band in the calculated spectrum is attributed to a one-electron π-π* transition, which is localized predominantly on the pyrazole ring and the C=N bond. This is also indicated by the values of charge localization and charge transfer, which are summarized in Table 3. The second experimentally observed band in the UV spectrum corresponds to a 0 → 4 electronic transition which is localized on the Ph_B phenyl radical.

The oxidation of compounds III to IV is reflected in the nature of the electronic spectra: the number of bands increases, the effect of substituents R^1 is voided, and the long-wavelength absorption band is shifted to the red relative to the spectra of compounds III. Compounds IV also exhibit fluorescence, with large values of the Stokes' shift (Table 2). All of these data are consistent with the formation of a polynuclear aromatic system.

The PMR spectra of comounds III, measured in $CDCl_3$ solution, contain in addition to a singlet for the methyl group (Table 1) and a multiplet for the aromatic protons (7.38-7.63 ppm), a doublet and triplet for the protons of the $CHCH_2$ fragment of the heterocycle; the simplified pattern of these signals is evidence of a high rate of inversion of the bicyclic ring system. This is furthermore consistent with analysis of Dreiding models of molecules

TABLE 3. Results of Spectral Calculations for a Model Molecule 

Electronic transition	UV spectral band	Calc.		Experimental		Localization, %				Charge transfer, %			
		E, eV	f	E, eV	f	Pyr	C=N	Ph_A	Ph_B	Pyr	C=N	Ph_A	Ph_B
0→1	1	3,73	0,82	3,73	0,70	37,4	25,7	19,2	17,7	−0,35	0,21	0,04	0,10
0→2		4,20	0,46			47,9	25,2	11,1	15,7	−0,55	0,36	0,04	0,15
0→3		4,45	0,027			13,5	1,83	83,7	0,9	−0,20	−0,01	0,21	−0,003
0→4	2	4,81	0,50	4,95	0,12	3,3	9.4	0,6	86,7	−0,01	0,08	0,002	0,07
0→5		5,16	0,025			46,3	12,3	31,3	10,1	−0,58	0,004	0,52	0,06

*Calculations were carried out using the Pariser–Parr–Pople (PPP) variant of MO LCAO self-consistent field configuration interaction (SCFCI) with a standard set of parameters.

TABLE 4. Mass Spectra of Compounds IIIa, k

Compound	m/e values (intensity, %)
IIIa	**363** (100), 348 (34), 286 (88), 260 (41), 259 (38), 218 (38), 115 (33), 104 (25), 103 (19), 77 (65)
IIIk	**408** (100), 378 (17), 336 (22), 331 (73), 285 (22), 104 (22), 103 (20), 102 (23), 91 (17), 77 (78)

*The 10 most intense peaks in the spectra are summarized; the m/e values of the molecular ions are shown in boldface type.

of III, which reveal that the bicycle exists in the twist-form, which upon the whole is flattened, but from which the $C_{(2)}$ and $C_{(3)}$ atoms are deflected from the average plane of the molecule of 0.2 and 0.4 Å, respectively.

Aromatization of compounds III is accompanied by simplification of their PMR spectra: the multiplets due to the $CHCH_2$ fragment are replaced in the spectra of compounds IV by a singlet for a pyridine ring proton at δ 7.29 ppm.

Mass spectra were obtained for compounds IIIa and IIIk; the most general characteristic of the mass spectra is the relatively high intensity of the molecular ion peaks (Table 4). The main fragmentation pathway involves cleavage of $C_6H_5^{\cdot}$, $C_6H_5CN^{\cdot}$, and C_6H_5CNH fragments, as well as of the methyl group in position 5.

In conclusion, it should be noted that according to previous reports [2], the reaction of unsymmetrically substituted β-diketones with aminoazoles leads to the formation of mixtures of isomers. The results obtained herein indicate that these products can also be prepared from α,β-unsaturated ketones. Since the reaction of these ketones with aminopyrazole appears to be regioselective, it must be regarded as a more promising method for the synthesis of condensed nitrogen-containing heterocycles.

EXPERIMENTAL

IR spectra of compounds III and IV for KBr pellets were measured on a Specord IR-75 spectrophotometer, electronic absorption spectra for methanol solutions were obtained on a Specord UV-VIS spectrophotometer, and fluorescence spectra were obtained for methanol solutions on an apparatus consisting of a monochromator, light source and a photomultiplier tube; PMR spectra of $CDCl_3$ solutions were obtained on a Bruker-100 spectrometer versus TMS as internal standard. Mass spectra were recorded on a Varian MAT-311A spectrometer in a standard working mode at an electron ionizing energy of 70eV. The purity of compounds was monitored by TLC on Silufol UV-254 plates with chloroform eluent.

5-Methyl-2,4,7-triphenyl-3,4-dihydropyrazolo[4,5-b]pyridine (IIIa). A solution of 0.3 g (1.7 mmole) 5-amino-3-methyl-1-phenylpyrazole and 0.36 g (1.7 mmole) chalcone IIa in 1 ml DMF was heated for 1 h. After cooling the reaction mixture was filtered to remove the precipitate which had formed; the latter was dissolved in chloroform and subjected to column chromatography on Al_2O_3 with chloroform eluent. The first fraction contained a luminescent product, IVa (monitored using a UV light source), while the second fraction contained compound IIIa. Solvent evaporation from the second fraction, followed by crystallization of the residue from methanol gave 0.41 g (65%) of compound IIIa, mp 136-137°C.

Compounds IIIb-k were prepared in an analogous manner.

5-Methyl-2,4,7-triphenylpyrazolo[4,5-b]pyridine (IVa). A. To a hot solution of 0.5 g (1.4 mmole) compound IIIa in 15 ml of methanol was added in two portions 0.5 g (2.4 mmole) of N-bromosuccinimide and the mixture was refluxed for 30 min. After cooling the reaction mixture, the resulting precipitate was removed by filtration, dissolved in chloroform, and chromatographed on an Al_2O_3 column. The first luminescent fraction contains compound IVa: 0.4 g (80%), mp 130-132°C (from methanol).

Compounds IVb-k were obtained in an analogous manner.

B. A solution of 0.3 g (1.7 mmole) amine I and 0.38 g (1.7 mmole) dibenzoylmethane V in 5 ml acetic acid was refluxed for 1 h. The mixture was then diluted with 5 ml water. The resulting precipitate was worked up by analogy with method A. Yield 3.2 g* (52%) of compound IVa.

C. A solution of 0.3 g (1.7 mmole) amine I and 0.63 g (1.7 mmole) 2,3-dibromo-1,3-diphenyl-1-propanol (VIa) in 3 ml DMF was refluxed for 1 h. Further workup was identical to that in method A. Yield 0.43 g (70%) of compound IVa.

Compound IVf was prepared in a similar manner (66% yield).

D. Under the same conditions as method B, amine I (0.3 g, 1.7 mmole) and the chalcone α-epoxide (0.38 g, 1.7 mmole) gave 0.3 g (50%) of compound IVa.

4,7-Diaryl-2,5-dimethylpyrazolo[4,5-b]pyridine (IVℓ). A solution of 0.3 g (1.7 mmole) 5-amino-3-methyl-1-phenylpyrazole and 0.25 g (1.7 mmole) benzalacetone in 1 ml DMF was heated for 1 h. After cooling the reaction mixture, the resulting precipitate was removed by filtration, dissolved in chloroform, and chromatographed on an aluminum oxide column with chloroform eluent. The solvent was evaporated and the residue was crystallized from methanol. Yield 0.29 g (60%) of compound IVℓ, mp 154-155°C.

LITERATURE CITED

1. S. V. Tabak, I. I. Grandberg, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 1, 116 (1965).
2. A. N. Kost, Khim. Geterotsikl. Soedin., No. 9, 1200 (1980).

* As in Russian original – Publisher.