REACTIONS OF 4,5-DIAMINOPYRAZOLES WITH CHALCONES AND ACETYLARENES

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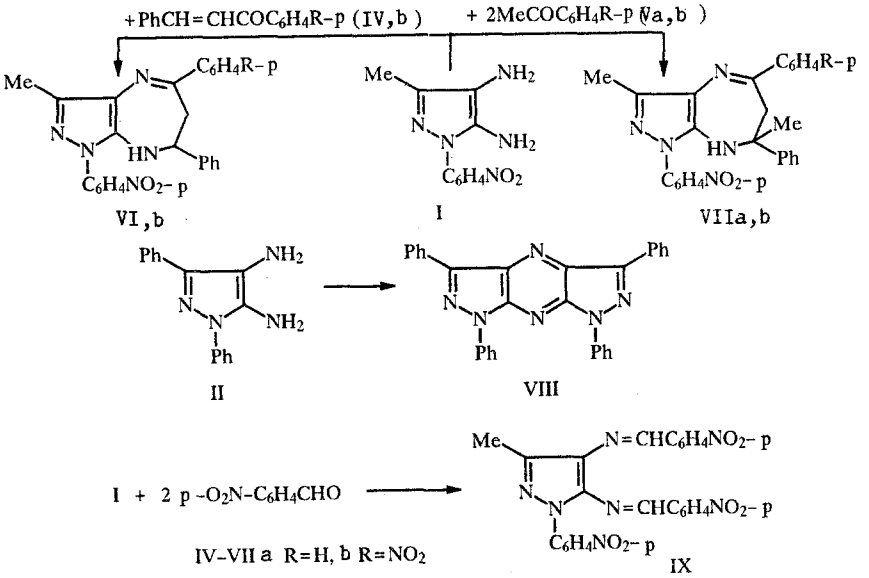
Reaction of 3-methyl-1-(4-nitrophenyl)-4,5-diaminopyrazole with chalcones and acetylarenes gave 1H-2,3-dihydropyrazolo[4,5-b]-1,5-diazepines. The structure of one of these was confirmed by x-ray analysis. 3,5-Diphenyl- and 3-oxo-4,5-diaminopyrazoles did not take part in this reaction.

The reactions of aromatic and heterocyclic 1,2-diamines with α,β-unsaturated ketones opens the way to the synthesis of 5-, 6-, and 7-membered nitrogen heterocycles [1]. A feature of these reactions is their high regioselectivity but the actual direction of the reaction is usually quite complex.

The aim of this work was a study of the reaction of 1-(4-nitrophenyl)-3-methyl- (I), 1,3-diphenyl- (II), and 3-oxo-4,5-diaminopyrazole (III) with chalcones IVa, b and acetylarenes Va, b and proof of the reaction course by x-ray analysis of one of the products. Instead of the usual systematic series of ketones traditional for such investigations we have studied the reaction of only the unsubstituted compounds and their nitro derivatives (showing the greatest reactivity toward nucleophiles).

Diamine I reacts with ketones IV and V in refluxing methanol solution in the presence of acetic acid. The 1H-2,3-dihydropyrazolo[4,5-b]-1,5-diazepines VIa, b and VIIa, b are formed in good yields.

Diamines II and III do not react with IV or V under these conditions or upon variation of the catalyst (HCl, triethylamine) or solvent (ethanol, propanol, toluene, diglyme). The ketones and diamine III remain unchanged in these experiments whereas diamine II gives 10-50% of the previously reported [3] bispyrazolo[3,4-b:4′,3′-e]pyrazine self-condensation product (VIII).



Formation of VIa, b and VIIa, b is supported by elemental analytical and spectroscopic parameters (Table 1), identical with analogous products obtained from 3-methyl-1-phenyl-4,5-diaminopyrazole [2]. Compounds VI and VII differ from those described in [2] only by the presence of nitro groups in the N-phenyl ring which gives rise to a 5-14 nm hypsochromic shift in the long-wavelength absorption. This is undoubtedly a result of the strong electron accepting effect of the N-nitrophenyl radical which weakens the π-electronic conduction of the pyrazole ring. As evidenced by quantum chemical calculations [2], this plays an important part in the 0—1 electronic transition.

The close comparison in synthesis conditions and properties of VI and VII with those reported [2] shows that their structures are the same. This was proved by x-ray structural analysis of VIa carried in Poznan University. The atomic coordinates for

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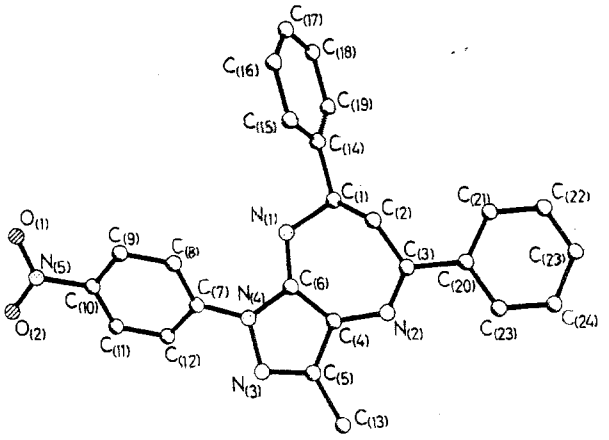

Fig. 1. Structure and numbering of the atoms in molecule VIa.

TABLE 1. Parameters for 1H-2,3-Dihydropyrazolo[4,5-b]-1,5-diazepines (VIa, b, VIIa, b) and Bisazomethine IX

Compound	Mp, °C	UV spectrum (in MeOH), λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)	IR spectrum, cm^{-1} KBr		Reflux time, h	Yield, %
			ν_{NO_2}	ν_{NH}		
VIa	165	350 (19,5) 253	1515, 1337	3363	2,5	55
VIb	228	415 (15,7) 341 (16,7) 257	1508, 1342	3336	1,5	75
VIIa*	185	345 (20,8) 260	1510, 1337	3361	2	45
VIIb	233...235	404 (13,7) 346 (14,4) 264 (19,8)	1515, 1337	3374	1	75
IX	257...258	407 (15,0) 327 (12,2)	1522, 1337	—	0,25	85

*In the PMR spectrum $\delta(CH_3)$ 1.64 and 2.46, $\delta(CH_2)$ 3.35, and δ(NH) 4.83 ppm.

TABLE 2. Nonhydrogen ($\times 10^4$) and Hydrogen ($\times 10^3$) Atomic Coordinates for VIa

Atom	$X(\sigma)$	$Y(\sigma)$	$Z(\sigma)$	Atom	$X(\sigma)$	$Y(\sigma)$	$Z(\sigma)$
O(1)	2090(1)	-2633(2)	9131(1)	C(21)	6147(1)	5321(3)	11254(1)
O(2)	2064(1)	-2713(2)	8069(1)	C(22)	6593(1)	6287(3)	11494(1)
N(1)	4348(1)	2176(2)	10120(1)	C(23)	7057(1)	6445(3)	11190(2)
N(2)	5597(1)	3215(2)	9777(1)	C(24)	7094(1)	5650(3)	10646(2)
N(3)	4636(1)	1004(2)	8559(1)	C(25)	6648(1)	4690(3)	10402(1)
N(4)	4318(1)	1081(2)	9063(1)	H(N)	396(1)	226(3)	1002(1)
N(5)	2276(1)	-2295(2)	8646(1)	H(1)	459(1)	410(2)	1044(1)
C(1)	4631(1)	3172(2)	10632(1)	H(2,1)	545(1)	323(1)	1132(1)
C(2)	5319(1)	2899(2)	10866(1)	H(2,2)	539(1)	189(2)	1086(1)
C(3)	5684(1)	3505(2)	10414(1)	H(8)	388(1)	-12(2)	996(1)
C(4)	5139(1)	2324(2)	9445(1)	H(9)	301(1)	-150(2)	978(1)
C(5)	5123(1)	1754(2)	8795(1)	H(11)	269(1)	-95(2)	775(1)
C(6)	4606(1)	1891(2)	9593(1)	H(12)	356(1)	47(2)	792(1)
C(7)	3782(1)	317(2)	8973(1)	H(13,1)	551(1)	135(2)	800(1)
C(8)	3621(1)	-267(2)	9525(1)	H(13,2)	597(1)	157(3)	866(2)
C(9)	3113(1)	-1091(2)	9414(1)	H(13,3)	565(1)	277(3)	833(1)
C(10)	2787(1)	-1343(2)	8756(1)	H(15)	453(1)	126(2)	1148(1)
C(11)	2932(1)	-759(2)	8203(1)	H(16)	407(1)	100(3)	1234(1)
C(12)	3430(1)	80(2)	8309(1)	H(17)	356(1)	299(2)	1262(1)
C(13)	5588(1)	1921(3)	8393(1)	H(18)	353(1)	496(2)	1201(1)
C(14)	4323(1)	3108(2)	11211(1)	H(19)	401(1)	499(2)	1114(1)
C(15)	4321(2)	1961(3)	11581(2)	H(21)	581(1)	525(2)	1144(1)
C(16)	4037(2)	1903(3)	12109(2)	H(22)	652(1)	684(2)	1190(1)
C(17)	3741(1)	3008(3)	12260(1)	H(23)	738(1)	708(2)	1134(1)
C(18)	3748(1)	4151(3)	11911(1)	H(24)	741(1)	575(3)	1040(1)
C(19)	4040(1)	4216(3)	11384(1)	H(25)	668(1)	418(2)	1000(1)
C(20)	6168(1)	4512(2)	10700(1)				

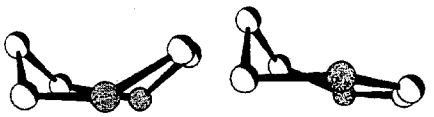

Fig. 2. Conformations of the 7-membered rings of 2,4-diphenyl-2,3-dihydro-1H-1,5-benzodiazepine (a) and VIa (b).

TABLE 3. Bond Lengths (d), Valence (β), and Dihedral (τ) Angles for the Heterocyclic Fragment of VIa

Bond	d, Å	Angle	β, degrees	Angle	τ, degrees
$N_{(1)}$—$C_{(1)}$	1,458(3)	$C_{(1)}N_{(1)}C_{(6)}$	119,7(2)	$C_{(6)}N_{(1)}C_{(1)}C_{(2)}$	-46,9(5)
$C_{(1)}$—$C_{(2)}$	1,535(3)	$C_{(2)}C_{(1)}N_{(1)}$	109,2(2)	$N_{(1)}C_{(1)}C_{(2)}C_{(3)}$	84,3(4)
$C_{(2)}$—$C_{(3)}$	1,506(3)	$C_{(3)}C_{(2)}C_{(1)}$	114,5(2)	$C_{(1)}C_{(2)}C_{(3)}N_{(2)}$	-59,8(4)
$C_{(3)}$—$N_{(2)}$	1,287(3)	$N_{(2)}C_{(3)}C_{(2)}$	123,5(2)	$C_{(2)}C_{(3)}N_{(2)}C_{(4)}$	1,7(4)
$N_{(2)}$—$C_{(4)}$	1,400(3)	$C_{(4)}N_{(2)}C_{(3)}$	121,9(2)	$C_{(3)}N_{(2)}C_{(4)}C_{(6)}$	21,3(4)
$C_{(4)}$—$C_{(6)}$	1,384(3)	$C_{(6)}C_{(4)}N_{(2)}$	132,5(2)	$N_{(2)}C_{(4)}C_{(6)}N_{(1)}$	-0,9(4)
$N_{(1)}$—$C_{(6)}$	1,372(3)	$N_{(1)}C_{(6)}C_{(4)}$	132,3(2)	$C_{(4)}C_{(6)}N_{(1)}C_{(1)}$	4,3(4)
$C_{(4)}$—$C_{(5)}$	1,400(3)	$N_{(3)}N_{(4)}C_{(6)}$	112,0(2)	$N_{(2)}C_{(3)}C_{(20)}C_{(25)}$	-25,7(4)
$C_{(5)}$—$N_{(3)}$	1,318(3)	$N_{(4)}C_{(6)}C_{(4)}$	106,4(2)	$C_{(2)}C_{(3)}C_{(20)}C_{(21)}$	-26,7(4)
$N_{(3)}$—$N_{(4)}$	1,391(2)	$N_{(4)}N_{(3)}C_{(5)}$	104,3(2)	$C_{(6)}N_{(4)}C_{(7)}C_{(8)}$	-33,7(4)
$N_{(4)}$—$C_{(6)}$	1,367(3)	$N_{(3)}C_{(5)}C_{(4)}$	112,3(2)	$N_{(3)}N_{(4)}C_{(7)}C_{(12)}$	-31,3(4)
$N_{(4)}$—$C_{(7)}$	1,406(3)	$C_{(5)}C_{(4)}C_{(6)}$	104,9(2)		
$C_{(5)}$—$C_{(13)}$	1,495(3)	$N_{(2)}C_{(3)}C_{(20)}$	119,8(2)		
$C_{(1)}$—$C_{(14)}$	1,509(3)	$N_{(3)}N_{(4)}C_{(7)}$	117,9(2)		
$C_{(3)}$—$C_{(20)}$	1,488(3)				

VIa are given in Table 2, the bond lengths, valence, and dihedral angles of the bicycle in Table 3, and the structure and numbering of the molecule in Fig. 1.

X-ray analysis particularly shows that the 4-amino group of diamine I forms the azomethine bond and that the 5-amino group adds to the C=C double bond of ketone IVa. This was confirmation of the correctness of the structural identities of dihydropyrazolodiazepine based on a comparison of experimental and calculated electronic absorption spectra of these compounds and azomethine models. For reactions of I this is the more important since the chemical properties of the amino groups are difficult to separate (as evidenced by the synthesis of the bisazomethine XI).

The pyrazole ring of VIa is planar and atoms N_1, N_2, C_3, and C_7 lie practically in that plane. There has recently appeared [5] a report of the x-ray analysis of a pyrazolo[4,5-b]-1-azepine dimer, in which there are two conformationally nonequivalent linkages of the pyrazole ring with the tetrahydrodiazepine. In one the 7-membered ring has a chair conformation and in the other a half chair. In spite of the significant structural differences between this dimer and VIa, the parameters (bond lengths, valence angles) of the pyrazole and adjacent bonds agree with an accuracy of ± 0.01 Å and $\pm 1°$, respectively. In VIa the N_4 atom deviates from the neighboring atomic plane by 0.044 Å.

Comparison of the structures of the 7-membered rings in VIa and 2,4-diphenyl-1H-2,3-dihydrobenzo[b]-1,5-diazepine [4] reveals a significant difference in the bond lengths and angles for the $N_2C_4C_6N_1$ portion. In spite of the similarity of the remainder of the 7-membered rings in these molecules, their conformations differ markedly (Fig. 2).

The benzannelated dihydrodiazepine ring has an approximately boat form whereas pyrazolodihydrodiazepine VIa is close to that of a "sofa" in which C_2 deviates from mean planarity by 0.977 Å. The C_3 phenyl fragment occupies a clearly defined equatorial position.

The ketonic activity of diamines II and III is significantly lower than indiamine I and its phenyl analog [2]. The thermodynamic stability of the 7-membered ring is not high as shown by the reaction of these compounds with aldehydes to give bisazomethines [2]. Exchange of the methyl group for a bulky 3-phenyl radical at the pyrazole 3 position must increase the instability of the neighboring 7-membered ring and, perhaps, cause the reaction of diamine II with ketones VI and VII to fail. The lower reactivity of the 4,5-diamino-3-pyrazolone is due to the electron acceptor effect of the oxo group which reduces the basicity of the amino function.

EXPERIMENTAL

The electron absorption spectra of VI, VII, and IX were measured in methanol solution for $2\text{-}4\cdot10^{-5}$ molar concentrations on a Specord UV-vis spectrometer. IR spectra were recorded for KBr tablets on a Specord IR-75 and the PMR spectrum of VIIa on a Tesla BS-2487 B (80 MHz) instrument using $CDCl_3$ solvent and TMS internal standard. Compound purity was monitored by TLC on Silufol UV-254 plates using benzene eluent.

Elemental analytical data for VIa, b, VIIa, b, and IX for nitrogen agreed with those calculated.

X-Ray Analysis of VIa. Crystals of VIa ($C_{25}H_{21}N_5O_2$, mol. wt. 423.5) were monoclinic. X-ray data: a = 22.669(5), b = 9.935(2), c = 20.240(3), β = 104.74(2)°, V = 4408.4(2) Å^3, d_{calc} = 1.37 g·cm^{-3}, Z = 4, μCuK_α = 8.0 cm^{-1}, space group C2/c. Measurement of the intensity of the diffracted light was carried out at 20°C on a four-circle automatic Syntex $P2_1$ diffractometer (λCuH_α, graphite monochromator, $\theta/2\theta$ scanning). The structure was solved by a direct method using the MULTAN program and refined by the least-squares method in a full matrix anisotropic approximation. The final difference factor was R = 0.042 (R_w = 0.041), calculated from 2029 reflections with $F \geq 6\sigma$. Hydrogen atoms were revealed in difference synthesis.

6-Methyl-2,4,8-diphenyl-(4-nitrophenyl)-1H-2,3-dihydropyrazolo[4,5-b]-1,5-diazepine (VIa). A solution of diamine I (0.7 g, 3 mmoles) and chalcone IVa (0.62 g, 3 mmoles) in methanol (15 ml) with acetic acid (1 ml) was refluxed for 2.5 h. The mixture was cooled, neutralized with aqueous ammonia, and left in the refrigerator for 1 h. The precipitate was filtered and recrystallized from hexane—benzene (1:2) to give VIa (0.7 g, 55%) with mp 165°C.

2,6-Dimethyl-2,4,8-diphenyl-(4-nitrophenyl)-1H-2,3-dihydropyrazolo[4,5-b]-1,5-diazepine (VIIa). Concentrated H_2SO_4 (2-3 drops) was added to a solution of diamine I (0.7 g, 3 mmoles) and acetophenone (0.7 g, 6 mmoles) in methanol (15 ml). The solution was refluxed for 2 h, neutralized with ammonia, and the crystals formed on cooling filtered to give VIIa (0.6 g, 45%) with mp 185°C (from benzene).

VIIb was obtained similarly.

4,5-Bis(4-nitrobenzylideneamino)-3-methyl-1-(4-nitrophenyl)pyrazole (IX). A solution of I (0.7 g, 3 mmoles), 4-nitrobenzaldehyde (0.64 g, 6 mmoles), and acetic acid (4-5 drops) in methanol (15 ml) was refluxed for 1 h and evaporated to 2/3 volume. Cooling and filtration of the precipitate gave IX (1.05 g, 85%) with mp 257-258°C (from hexane—benzene, 1:1).

LITERATURE CITED

1. V. D. Orlov and N. N. Kolos *Journal of Kharkov State University*, No. 319, 62 (1988).
2. V. D. Orlov, Kh. Kiroga, and N. N. Kolos, *Khim. Geterotsikl. Soedin.*, No. 3, 363 (1987).
3. V. D. Orlov, Kh. Kiroga, and N. N. Kolos, *Khim. Geterotsikl. Soedin.*, No. 9, 1222 (1988).
4. Z. Kaluski, É. Gzhesyak, V. D. Orlov, and N. N. Kolos, *Zh. Strukt. Khim.*, **30**, 187 (1989).
5. G. Daidone, V. Sprio, S. Plescia, M. L. Marino, G. Bombieri, and G. Bruno, *J. Chem. Soc., Perkin Trans. II*, No. 1, 137 (1989).