REACTION OF 5-HYDROXYPYRAZOLIDINES WITH HETARYLAMINES

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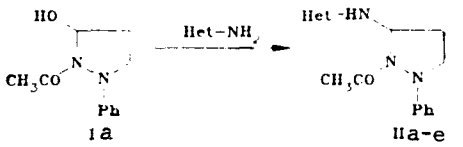
The reaction of 1-acetyl-5-hydroxypyrazolidines with heterocyclic compounds, the amino group of which has an aniline or amidine character, is regioselective and results in the formation of the corresponding hetarylaminopyrazolidines.

We have previously shown that the hydroxy group of 5-hydroxypyrazolidines having aminal properties readily undergoes nucleophilic substitution, particularly by amino [1] and hydrazino groups [2]; the thus-formed aminopyrazolidines have a cyclic structure, while the hydrazino derivatives exist preferentially in linear form [2, 3]. The present work deals with the investigation of the reaction of hydroxypyrazolidines with amine of the heteroaromatic series.

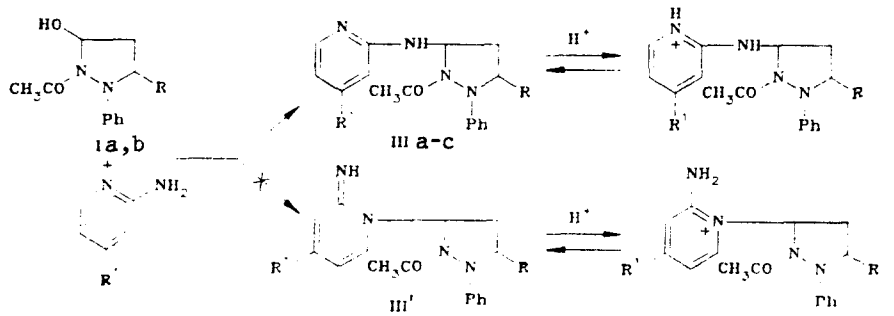
We showed that the amino derivatives of pyridine and quinoline in which the amino group displays properties similar to those of the anilino group – 3-aminopyridine, 3-aminoquinoline, 5-aminoquinaldine – react with 1-acetyl-2-phenyl-5-hydroxypyrazolidine (Ia) with the formation of hetarylaminopyrazolidines IIa-c, but the reaction requires longer times than the reaction with anilines (see Table 1).



II: a) Het = 3-pyridyl; b) Het = 3-quinolyl; c) Het = 2-methyl-5-quinolyl

According to PMR spectral data (see Table 1), the obtained compounds have a cyclic structure (a signal of the 5-H proton of the pyrazolidine ring at 5.8-6.3 ppm). Moreover, taking compound IIa as an example, we showed that the protonation of these systems proceeds at the pyridine ring, i.e., it does affect the pyrazolidine ring and the amino group (see the PMR spectrum with the addition of CF_3COOH). This renders the produced hetarylaminopyrazolidines stable in acid media, unlike other 5-functionally substituted pyrazolidines which decompose in acids [1].

2-Aminopyridine, the amino group of which is conjugated with the ring, has two reaction centers – the nitrogen atoms – and can react variably with hydroxypyrazolidines [4, 5]. Nevertheless, the reaction of 2-aminopyridine and 2-amino-4-methylpyridine with hydroxypyrazolidines proceeds regioselectively with the formation of cyclic derivatives of pyrazolidine III or III'. The PMR spectra of an acidified solution also indicate protonation in the pyridine ring (see Table 1).



I a R=H; b R=CH_3; III a R=R'=H; b R=H, R'=CH_3; c R=CH_3, R'=H

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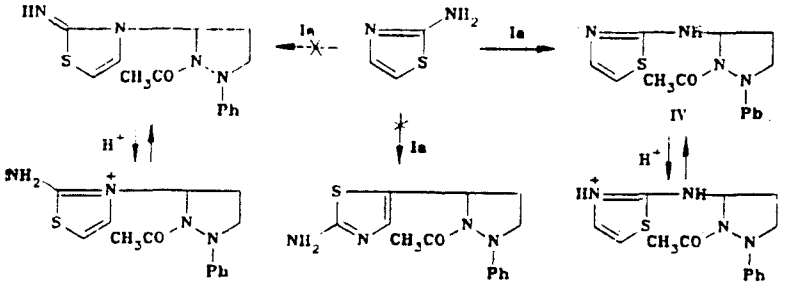
TABLE 1. Characteristics of Obtained Compounds

Compound	Empirical formula	Time of reaction, h	mp, °C	IR spectrum, cm^{-1}	UV spec., λ_{max}, nm (log ε)		PMR spectrum, δ, ppm							Yield, %
					in $CHCl_2$	in $CHCl_2$+ HCl	solvent	CH_3CO, s	3-H, m	4-H, m	5-H, m	NH, br.s	Het	
IIa	$C_{16}H_{18}N_4O$	8	184...185	3275, 1660	242 (3,94); 291 (4,49)	242 (3,94); 291 (4,49)	$CDCl_3$	2,00	3,50	2,15	5,85	5,85	6,46...7,33 (m); 7,80 (d, α-H Py)	69
							$CDCl_3$+ CF_3COOH	2,00	3,50	2,15	5,85	—	6,60...8,80 (m); 8,56 (d, α-H Py)	—
IIb	$C_{20}H_{20}N_4O$	20	202...203	3260, 1670	—	—	DMSO-D_6	1,94	3,56	2,10	5,85	6,80	6,45...7,70 (m); 8,16 (d, α-H Qu)	35
IIc	$C_{21}H_{22}N_4O$	11	193...194	3320, 1640	—	—	$CDCl_3$	2,15	3,70	2,25	6,30	—	6,80...7,80 (m); 2,70 (s, 3H)	37
IIIa	$C_{16}H_{18}N_4O$	10	139...140	3340, 1650	242 (4,52); 291 (4,09)	242 (4,52); 291 (4,09)	$CDCl_3$	2,10	3,50	2,20	6,10	4,70	6,70...7,10 (m); 7,46 (d, α-H Py)	47
IIIb	$C_{17}H_{20}N_4O$	18	162...163	3340, 1650	—	—	$CDCl_3$	2,05	3,50	2,43	6,10	4,70	6,60...7,20 (m); 7,90 (d, α-H Py); 2,25 (c, 3H)	51
IIIc	$C_{17}H_{20}N_4O$	48	183...184	3330, 1640	—	—	$CDCl_3$	2,10	3,95; 1,30 (d, 3H)	2,20	6,10	4,70	6,35...7,20 (m); 7,80 (d, α-H Py)	—
							$CDCl_3$+ CF_3COOH	2,10	3,95; 1,30 (d, 3H)	2,20	6,10	4,70	6,60...7,80 (m); 8,57 (d, α-H Py)	38
IV	$C_{14}H_{16}N_4OS$	18	173...174	3400, 1670	241 (4,26)	241 (4,23)	$CDCl_3$	2,15	3,55	2,20	6,05	6,15	6,80...7,4 (m); 6,53 (d, 5-H Tz)	53

*Compounds IIa, IIIa were recrystallized from benzene, IIb from acetone, IIc, IIIb, c, and IV from a benzene–ether mixture.

The UV spectrum of compound III(III')a remains the same on changing from a neutral solvent (CH_2Cl_2) to a solvent acidified with HCl (see Table 1), which, taking into account the direction of the protonation, makes it possible, in analogy with the data in [6], to make a definite choice in favor of the amino derivatives IIIa-c.

2-Aminothiazole has three possible reaction centers in the molecule, two nitrogen atoms and a $C_{(5)}$ atom, and an aminomethylation reaction at the 5-position has been described [7]. However, the spectral data show that only the amino derivatives IV are formed in this case also – in the PMR spectrum there are signals of the 5-H proton of pyrazolidine at 6.05 and 5-H of thiazole at 6.53 ppm, and as in the case of aminopyridines there are no changes in the UV spectrum on changing from a neutral to an acidified solution (see Table 1).



Thus, the reaction of hydroxypyrazolidines with heterocyclic amines gives the corresponding amino derivatives of pyrazolidine only.

EXPERIMENTAL

The IR spectra of the compounds were run on UR-20 and Specord IR-75 spectrophotometers in the form of a suspension and in mineral oil, and in CH_2Cl_2 solutions. The UV spectra were run on a Cary-40 spectrophotometer in methylene chloride solutions. The PMR spectra were recorded on a Tesla BS-467A spectrophotometer (60 MHz) with TMS as internal standard. The course of the reactions and the purity of the obtained products was monitored by TLC on Silufol UV-254 plates in a benzene–ethyl acetate (1:1) system.

The data of the elemental analysis of all the synthesized compounds for C, H, N correspond to the calculated values.

(1-Acetyl-2-phenyl-5-pyrazolidinyl)amino Derivatives of Heterocycles. A mixture of equimolar amounts of hydroxypyrazolidine I and the corresponding amino derivative in benzene, 1:10 is boiled (see Table 1). At the end of the reaction, the solvent is evaporated, and the residue is triturated with ether. The hetarylamines are purified by recrystallization.

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