INTRODUCTION OF THE PYRAZOLIDINE RING INTO THE PYRROLE RING OF INDOLE

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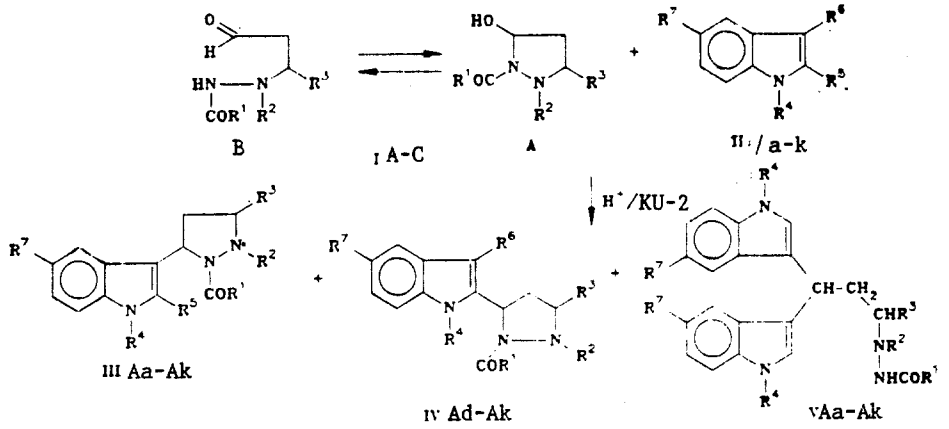
The reaction of indoles with 1-acyl-5-hydroxypyrazolidines under heterogeneous catalysis conditions leads, depending on the structure of indole, to 2- and/or 3-(1-acyl-5-pyrazolidinyl)indoles. Thus, the formation of 2-pyrazolidinylindoles is the results of an unco-substitution at the 3-position of the indole, followed by migration of the pyrazolidine ring.

It is known that amidoalkylation of indoles occurs in the pyrrole ring at the 3- [1] or 2-position [2], while in a strongly protonating medium it takes place at the 5- or 6-position of the benzene ring [3]. The amidoalkylation with cyclic carbinolamides – 1-acyl-5-hydroxypyrazolidines [4] – which recently became available, seems promising since it opens a route for the preparation of new heterocyclic systems – the azolylindoles.

Reaction of 1-acyl-5-hydroxypyrazolidines (I) with indoles II proceeds under very mild conditions – with a heterophase acid catalysis (KU-2 ion-exchange resin in the H^+-form), and the paths of the reaction may differ depending on the structure of the pyrrole moiety of indole:



Compound II-V	R^4	R^5	R^6	Compound II-V	R^4	R^5	R^6	Compound II-V	R^4	R^5	R^6
a	H	H	H	e	CH_3	H	CH_3	i	H	CH_2Ph	H
b	H	CH_3	H	f	H	H	Ph	j	CH_3	H	H
c	H	CH_3	H	g	H	H	CH_2Ph	k	CH_3	CH_3	H
d	H	H	CH_3	h	H	Ph	H				

The reaction of 1-acetyl-2-phenyl-5-hydroxypyrazolidine (IA) and unsubstituted indole (IIa) (ratio 1:2) results in the formation of a mixture of two compounds – the expected 3-pyrazolidinylindole (compound IIIAa) and bis-indolylhydrazinopropane (compound VAa). The spectral characteristics of 3-pyrazolidinylindole indicate a vinylogy characteristic for 3-functional derivatives of indole: Thus, the CS of the 5-H proton signal in the PMR spectrum of this compound (~5.8 ppm) differs little from that in the initial 5-hydroxypyrazolidine (~6 ppm), while the absorption band of the indole NH group in the IR spectrum (3250 cm^{-1}) has an aminic character. The absence of the 3-H signal of indole in the PMR spectrum, the CS of signals of the $C_{(3)}$ atoms of indole at 115 and $C_{(5)}$ of pyrazolidine at 54 ppm in the ^{13}C NMR spectrum are also characteristic and confirm the introduction of the pyrazolidine ring into the 3-position of the indole ring.

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TABLE 1. Results of Reaction of Compounds I with Indoles

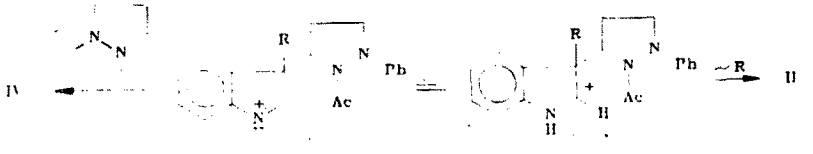
Compound	Indole	Time of reaction, h	Yield of compounds, % III	IV	V	Compound	Indole	Time of reaction, h	Yield of compounds, % III	IV	V
IA	IIa	10	25	—	31	IA	IIf	4	—	59	—
IB	IIa	20	15	—	26	IA	IIg	4	5	66	—
IC	IIa	5	29	—	31	IA	IIh	6	—	39	—
IA	IIb	13	21	—	36	IA	IIi	6	—	46	—
IA	IIc	12	27	—	28	IA	IIj	6	Traces	30	14
IA	IId	2	—	87	—	IA	IIk	6	18	15	15
IA	IIe	3	—	82	—						

The second compound obtained in the reaction of indole with hydroxypyrazolidine IA probably forms as the result of a reaction of two molecules of indole with an open tautomeric form of compound IA. This compound has the structure of bis-indolyl-3-alkane usual for the reaction products of indoles with aldehydes: The 3-H proton signal of the indole ring (6.0-6.5 ppm) is absent in the PMR spectrum, and two singlet signals of the acetyl group protons are observed at 1.9 and 2.0 ppm, clearly caused by an inhibited rotation around the C–N bond of the hydrazide (1:1 ratio of the isomers).

The reaction of indole with hydroxypyrazolidines IB, C proceeds in a similar way, with the ratio of the mono- and bis-addition products varying only according to the duration of the reaction (Table 1). Despite the fact that, for the hydroxypyrazolidine IC, the presence of a considerable amount of the open form was detected in the solution [5], the yield of the bis-derivative was not greater. However, during the slowing down of the main reaction (compound IB), the content of bis-indolylhydrazinoalkane VBa increases. The results of the condensation of pyrazolidine IA with 2-methyl- and 2,5-dimethylindoles (IIb, c) also do not differ from those for indole and comprise the corresponding mono- and bis-indole derivatives (see Tables 1 and 2).

When 3-substituted indoles with a free 2-position are used (compounds IId-f) only 3-R-2-(1-acetyl-5-pyrazolidinyl)indoles IV are formed rapidly and in good yields (Tables 1 and 2). In the IR spectra of 2-pyrazolidinylindoles with a free NH group, the formation of a strong intramolecular hydrogen bond was recorded between the indole NH proton and the amide carbonyl group of pyrazolidine (absence of a concentrational dependence). The 5-H proton signals of pyrazolidine in the PMR spectra of these compounds are present in a stronger field (–4.5 ppm) than in the case of the 3-isomers (see Table 2), while in the ^{13}C NMR spectrum of compound IVAd the corresponding carbon atom has a signal in the 33-ppm region (see Table 3). Thus, the data of the NMR spectra and, in particular, the 5-H and $C_{(5)}$ signals of the pyrazolidine ring may serve as a criterion for assigning the pyrazolidinylindoles obtained to the 2- or 3-series.

In the amidoalkylation reactions [2], the formation of the 2-substituted indoles in the presence of a substituent at the 3-position was considered to be the result of the direct attack of the cation of the amidoalkylating agent at the 2-position. However, when 3-benzylindole (IIg) was used in the present reaction, we isolated not only the 2-pyrazolidinyl derivative IVAg, but also an appreciable amount of a second compound – 3-pyrazolidinyl-2-benzylindole (IIIAg), while 3-benzylindole itself did not isomerize under these conditions. Hence, the primary event in this process is an unco-attack at the most nucleophilic position 3 of the indole, followed by a competitive migration taking place in the indoleninium cation formed of he two gem-substituents according to the Plancher rearrangement known for alkylindoles [6]:



The above data show that the ability of the pyrazolidine ring to migrate is considerably higher under these conditions than in the case of the relatively readily migrating benzyl and phenyl radicals [7]. The result is that in the reaction of hydroxypyrazolidine IA with 2-benzyl- and 2-phenylindoles (IIh, i) instead of the expected 3-pyrazolidinyl-2-R-indoles III, we obtained the product of a double Wagner–Meerwein rearrangement – the isomeric 3-R-2-pyrazolidinylindoles IVAh, Ai which were identical with the compounds obtained from 3-substituted indoles. A small number of such double migrations is known, and they occur under very rigorous conditions [8].

Introduction of the N–CH_3 group into the molecule of indole with a free 3-position (compounds IIj, k) led not only to the expected increase in rate, but also to a change in the direction of the process. Thus, by reacting N-methylindole (IIj) with hydroxypyrazolidine IA, the 3-isomer is obtained in trace amounts (PMR), and compounds IVAj and VAj are the two main reaction products (see Table 1), while in the case of 1,2-dimethylindole (IIk), all three reaction paths are obtained. On acid cataly-

TABLE 2. Characteristics of Compounds III-V

Compound	Empirical formula	R_f	mp, °C	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)					
					R^1, s	$-CH_2-$, m	CHR^3, m	CH	R^2, Ar, m	R^4-R^7 (NH)
IIIAa	$C_{19}H_{19}N_3O$	0,58	183...184	3250, 1650	2,17	2,60	3,61; 3,95	5,86 d.d(7)	6,90...7,40; 7,8 (4-H)	8,2 br.s
IIIBa*	$C_{20}H_{21}N_3O$	0,60	174...176	3270, 1660	1,83	2,26	4,26	5,65d.d (7)	6,60...7,70	1,22 d (8)
IIICa*	$C_{24}H_{23}N_3O$	0,67	144...145	3280, 1680	—	2,80	3,80	5,70d.d (6)	3,0 s, 6,9...7,8	—
IIIAb	$C_{20}H_{21}N_3O$	0,71	169...171	3300, 1660	2,10	2,30	3,75	5,72 d.d(8)	6,9...7,3	2,6 s
IIIAc	$C_{21}H_{23}N_3O$	0,62	224...226	3310, 1650	2,06	2,40	3,45...4,3	5,57 d.d(9)	6,65...7,40	2,13 s 2,6 s; 8,00 br.s
IIIAj	$C_{26}H_{25}N_3O$	0,66	187...188	3250, 1675	2,10	2,19	3,65	5,85 d.d(8)	6,80...7,70	4,2 s
IIIAk	$C_{21}H_{23}N_3O$	0,60	148...150	1650	1,98	4,25; 4,63	3,44; 4,1	5,50 d.d(9)	6,6...7,3	2,52 s
IVAd	$C_{20}H_{21}N_3O$	0,48	198...200	3400, 3280, 1650	2,04; 2,15	2,12	3,3...3,7	4,37 d.d(4)	6,7...7,6	2,31 s 2,37 s
IVAe (Ak)	$C_{21}H_{23}N_3O$	0,37	114...115	1700	2,06; 2,12	2,20	3,6	4,60 m	6,6...7,65	4,45 s, 3,55 s, 2,2 s, 2,3 s
IVAf (Ah)	$C_{25}H_{23}N_3O$	0,53	227...228	3400, 3290, 1690	2,00; 2,15	2,10	3,3	4,4 d.d(6)	6,43...7,5	9,9 br.s
IVAg* (Ai)	$C_{26}H_{25}N_3O$	0,56	205...206	3400, 3280, 1700	1,92	2,40	3,3...3,7	4,42d.d (8; 9)	6,15...7,35	4,1 s 9,9 br.s
IVAj	$C_{20}H_{21}N_3O$	0,42	178...180	1660	2,10; 2,16	2,35	3,2...3,6	4,46 d.d(7)	6,6...7,7	3,68 s, 3,70 s; 6,24 s (3-H)
VAa	$C_{27}H_{26}N_4O$	0,42	149...150	3400, 3320, 1700	1,96; 2,03	2,24	3,46	4,34 m	6,5...7,5	7,95 br.s
VBa*	$C_{28}H_{28}N_4O$	0,45	154...156	3460, 3280, 1670	1,90; 1,92	2,26	4,20	4,5 m	6,6...7,3	1,2 d (7); 7,7 br.s
VCa*	$C_{33}H_{30}N_4O$	0,55	183...185	3460, 3300, 1680	—	2,56	3,4	4,45 m	3,5 s; 6,8...7,6	7,7 br.s
VAb	$C_{29}H_{30}N_4O$	0,40	144...146	3430, 3300, 1690	2,00; 2,05	2,10	3,46	4,30m	6,6...7,3	2,2 s, 2,3 s; 7,95 br.s
VAc	$C_{31}H_{34}N_4O$	0,48	160...161	3460, 3280, 1665	2,10; 2,13	2,30	3,60	4,35m	6,8...7,5	2,10 s 2,14 s; 2,50 s, 2,54 s, 8,0 br.s
VAj	$C_{29}H_{30}N_4O$	0,50	167...169	3260, 1700	1,90; 1,93	2,43	3,46	4,40m	6,5...7,57	3,50 s, 3,53 s, 7,8 br.s
VAk	$C_{31}H_{34}N_4O$	0,57	120...123	3300, 1660	2,00; 2,16	2,10	3,50	4,46m	6,6...7,35	2,20 s 2,30 s, 3,60 s, 3,65 s, 7,8 br.s

*The PMR spectrum was run in DMSO-D_6; the remainder were run in $CDCl_3$.

TABLE 3. ^{13}C NMR Spectra of Pyrazolidinylindoles*

Compound	δ, ppm																		
	Pyrazolidine ring					Indole ring								phenyl ring**					
	CH_2CO	4	3	5	R	2	3	3a	4	5	6	7	7a	*i*	*o*	*m*	*p*	C=O
IIIAa	21,50	32,56	53,20	53,57	—	122,19	115,75	126,32	119,66	119,98	121,17	111,03	136,39	150,58	115,26	128,90	122,65	178,35
IIIAb	21,31	33,20	54,42	56,91	12,30	121,55	115,56	128,95	118,71	119,84	120,59	110,20	135,38	151,10	115,04	129,16	121,30	173,08
IVA	21,04	28,69	48,05	34,31	8,49	136,06	112,94	129,01	118,58	118,78	120,68	110,95	138,40	145,93	114,34	129,31	124,23	170,16
IVAg (Ai)	20,76	30,09	52,52	33,56	31,70; 128,33; 126,47	135,95	111,67	128,78	118,91	119,24	120,09	110,80	139,97	145,93	117,72	129,04	124,99	168,25
IVAj	20,74	28,99	47,88	33,43	32,52	129,17	109,68	126,83	118,42	118,87	121,04	111,79	137,00	145,96	117,68	128,47	125,06	168,33

*The spectra of compounds IIIAa, Ab and IVAd were run in $CDCl_3$ and those of compounds IVAg(i) and IVAj in DMSO-D_6.

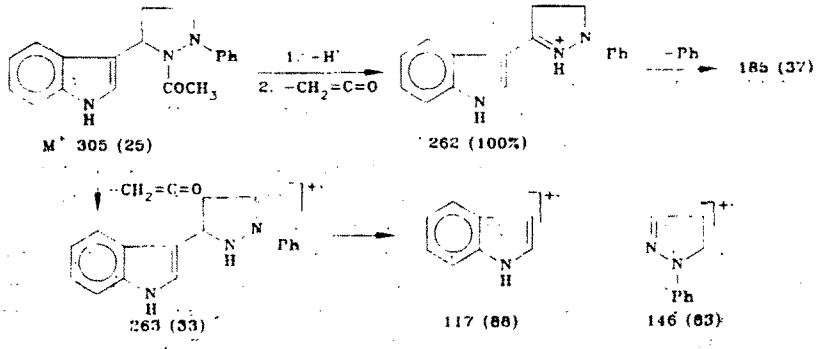
**The assignment of signals with similar CS in the aromatic region may be equivocal.

sis, pure 1,2-dimethyl-3-pyrazolidinylindole (IIIAk) converts slowly and only to a small extent into the isomeric 2-pyrazolidinylindole IVAk, since the possibility of this transformation sharply decreases because of the preferential protonation of the pyrazolidine and not the indole fragment. Thus, also under these conditions, isomerization probably results from the initial attack of the cation at the 3-position of indole.

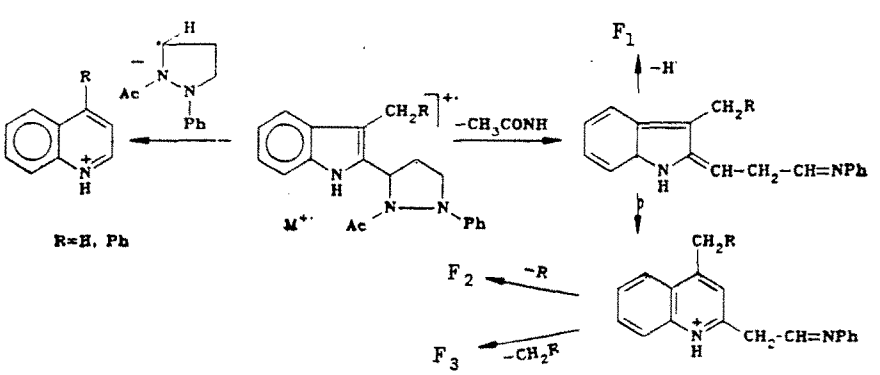
The 2-pyrazolidinyl derivatives of indoles are more stable than the 3-substituted derivatives in the solid phase and in solutions. The higher stability of 2-pyrazolidinylindoles is particularly indicated by the intensities of the molecular ions in the mass spectra, which are much higher for the 2-substituted derivatives (see Table 4). It is possible that this factor is one of the main reasons for the occurrence of the rearrangements during the formation of 2-isomers, and also for the increase in the reaction rate of the 3-substituted indoles with pyrazolidines and, as a result, the absence of bis-derivatives V in the reaction mixture.

The differences in the behavior of the obtained indole derivatives III, V, and IV under the action of electron impact are quite considerable: While bis-indolylhydrazinopropanes V are characterized by a fragmentation characteristic for noncyclic derivatives of hydrazine [9] with direct splitting of an acetylphenylhydrazine molecules (for compound VAj ion 300,* I 33%), a splitting of the N–N (391, I 2%) and β-C–C bonds (287, I 18%) of the alkylhydrazine fragment and loss of an indole molecule (319, I 11%), the mass spectral data for pyrazolidinylindoles IIIAa and IVAd, Af(h) indicate their cyclic nature (see Table 4).

In the mass spectrum of 3-pyrazolidinylindole IIIAa a peak of a molecular ion is observed (I 25%), which decomposes by two paths: 1) elimination of hydrogen at the first stage of the reaction, followed by elimination of ketene, leading to the formation of an exceptionally stable 3-(β-indolyl)pyrazolinium cation with maximal intensity in the mass spectrum; 2) loss of ketene from M^+ and dissociation of the ion radical formed into two halves – the indole and pyrazolidine moieties:



The fragmentation of the molecular ion of 2-pyrazolidinyl derivatives IVAd, IVAg(i) is entirely different: The peak of the molecular ion is fairly intense (I 57 and 64%, respectively), and in contrast to 3-isomers, the 1-acylpyrazolinium cation is eliminated or undergoes opening of the pyrazolidine ring with splitting of the N–N bond. This path of dissociation is possibly due to the fact that a stable cation of the 3-(β-indolyl)pyrazolinium type cannot be formed:



Thus, the character of the decomposition of pyrazolidinylindoles is dependent on the structure of the compounds and, similarly as the NMR spectral data, is a criterion for assigning the compounds to the 2- or 3-series.

It should be noted that we were unable to react hydroxypyrazolidine with 2,3-dimethylindole, the reaction with the benzene ring also not being possible.

*Here and below the m/z values are given for the ion peaks.

TABLE 4. Mass Spectra of Indole Derivatives

Compound	m/z (I, %)*
IIIAa	305 M+ (25), 304 (33), 263 (33), 262 (100), 185 (37), 157 (50), 156 (58), 146 (83), 130 (46), 129 (83), 117 (88)
IVAd	319 M+ (57), 261 (58), 260 (36), 259 (68), 246 (15), 245 (37), 218 (22), 217 (23), 204 (10), 145 (30), 130 (100)
IVAg (Ai)	395 M+ (64), 337 (36), 336 (14), 335 (17), 259 (28), 246 (18), 245 (43), 221 (12), 206 (32), 130 (100)
VAj**	391 (2), 319 (11), 300 (33), 287 (18), 273 (100), 170 (28), 156 (28), 145 (16), 144 (26), 131 (30)

*The M^+ and 10 of the most intense peaks are given.

**The mass spectrum, obtained by chemical ionization, contains a peak 451 ($M^+ + 1$).

EXPERIMENTAL

The IR spectra were run on UR-20 and Specord IR-75 spectrophotometers in mineral oil and in CH_2Cl_2. The PMR spectra were measured on Tesla BS-467A (60 MHz), Bruker HX-90 and Bruker WM-250 spectrometers, using TMS as internal standard. The ^{13}C NMR spectra were obtained for concentrated (3 moles/liter) solutions on Varian FT-80 and Bruker HX-90 spectrometers (22.63 MHz) in a pulse regime with Fourier transformation under the conditions of noise uncoupling from protons. The mass-spectral investigations were carried out on MKh-1303 and Varian-MAT-111 mass spectrometers with introduction of the material into the ionic source at temperatures close to the melting points of the samples. The ionizing voltage was 70 eV and the emission current 1.5 mA. The course of the reaction and the purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates in a benzene–ethyl acetate (1:1) system.

General Procedure. A 2-mmole portion of 5-hydroxypyrazolidine IA-C and 2 mmoles of indole (for indoles IIa-c, j, k – 4 mmoles of indole) were dissolved in 30 ml of absolute methylene chloride, and 20 mg of KU-2 ion-exchange resin in the H^+ form was added. The reaction mixture was stirred for 2-13 h (for hydroxypyrazolidine IB stirring for 20 h is required), monitoring the course of the reaction by TLC. The resin was separated, the solvent was evaporated, and the residue was recrystallized from a chloroform–hexane mixture (for indoles IId, e) or chromatographed on a column with silica gel (40 × 100, eluent benzene–ethyl acetate, 1:1).

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