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XXX.* REARRANGEMENT OF 1-ARYL-2-ACYLPYRAZOLIDINES TO TETRAHYDROPYRIMIDO[1,2-a]INDOLES

Yu. N. Portnov, G. A. Golubeva, and A. N. Kost

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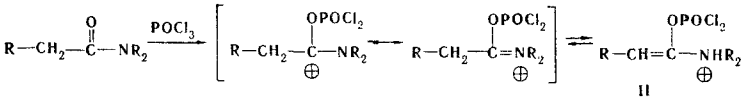
Rearrangement to form salts of substituted 1,2,3,4-tetrahydropyrimido[1,2-a]indoles occurs during the action of $POCl_3$, PCl_3, or PBr_3 on 1-aryl-2-acylpyrazolidines that have a methylene group in the α position of the acyl fragment. The resulting salts are readily converted to 10-hydroxy-2,3,4,10-tetrahydropyrimido[1,2-a]indoles by decomposition with aqueous alkali. The structures were proved by chemical transformations, UV, IR, PMR, and mass spectra, and alternative synthesis.

1-Arylpyrazolidines, the synthesis of which we described in [2], are easily added to activated triple bonds through the NH group to form enehydrazines, which are rearranged to 1-(3-aminoalkyl)indoles by the action of acidic agents. 1-Arylpyrazolidines react similarly with carbonyl compounds [3]. In the present paper, we have studied the action of acidic agents on 1-aryl-2-acylpyrazolidines, in which, as in enehydrazines, the unshared pair of electrons of the nitrogen atoms is conjugated with the π electrons of the double bond, but the π electrons of the carbonyl group rather than the double bond participate in this system of $p-\pi$ conjugation. In [4], it was demonstrated that dialkylamides can react with $POCl_3$ to form mesomeric cations I or II, which are capable of various condensations.



II

It might have been expected that electrophilic attack of phosphorus halides for compounds for the III type, in which the basicity of both nitrogen atoms is weakened due to $p-\pi$ conjugation with the aromatic system and the carbonyl group, would be directed to the oxygen atom. The resulting cation (IV) can then undergo intramolecular condensation of the electrophilic substitution type to form indazole derivative V or isomerize to enehydrazine VI, which is subsequently converted to VIII via the Fischer rearrangement, with the difference that, instead of elimination of the amino group, the intermediate state (VII) is stabilized due to cleavage of the more polar phosphate group (see Scheme A on following page). Several other processes leading to cleavage of the N–N bond (which is known for acylhydrazines [5]) might have been assumed. It was found that refluxing of 1-aryl-2-acylpyrazolidines with excess $POCl_3$ in ether for 12-24 h leads to high yields of saltlike substances that do not contain (according to elementary analysis) oxygen but do have two nitrogen atoms. The broad absorption band characteristic for the ammonium group is observed at 2750-3100 cm^{-1} in the IR spectra of these compounds, which made it possible to assume that the rearrangement proceeds to form compounds of the V or VIII type. The UV spectra of these compounds were found to coincide with the spectra of 2-aminoindole hydrohalides (λ_{max} 210-218, 260-270 nm), and the band at 260 nm in some of the compounds is split into two bands of equal intensity. The intense absorption at 1685-1700

*See [1] for communication XXIX.

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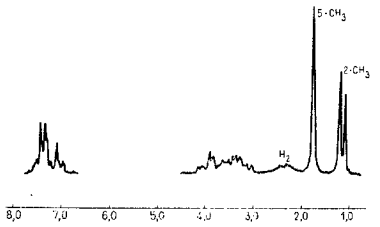
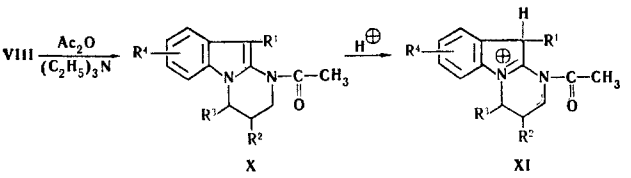


Fig. 1. PMR spectrum of XIIIa in CF_3COOH.

cm^{-1} in the IR spectra is also characteristic for 2-aminoindole salts and corresponds to the stretching vibrations of the C = N group [6, 7]. Additional arguments in favor of structure VIII were obtained from an analysis of the PMR spectra and chemical transformations. The PMR spectrum of VIIIa ($R^1 = R^2 = CH_3$, $R^3 = R^4 = H$) in CF_3COOH solution has a doublet from the 3-CH_3 group (3H, 1.1 ppm), a doublet from the 10-CH_3 group (3H, 1.55 ppm, J 7.6 Hz), a multiplet from the proton attached to C_3 (1H, 2.28 ppm), a multiplet from the proton attached to C_3 (1H, 2.28 ppm), a multiplet from five protons attached to C_2, C_4, and C_{10} (3.02-4.18 ppm), a multiplet from four aromatic protons (7.10-7.30 ppm), and a broad signal from the proton attached to the nitrogen atom (1H, 8.45 ppm). The character of the spectrum does not change in H_2O, but splitting of the signal from the 10-CH_3 group (a singlet with δ 1.72 ppm) vanishes in D_2O because of rapid deuterium exchange of the proton in the 10-position. It is known that 2-aminoindole salts exist primarily in the 2-iminoindolenine form (the VIII type) [6]; i.e., delocalization of the charge in the amidine system of bonds gives a greater gain in energy than during the formation of an aromatic pyrrole ring in IX. Hence, the extreme lability of the proton attached to the carbon atom between the benzene ring and the protonated amidine grouping becomes understandable. Compounds VIII are readily acetylated under mild conditions to form acetyl derivatives (X).



The UV spectrum of Xa ($R^1 = R^2 = CH_3$, $R^3 = R^4 = H$) contains two maxima with λ_{max} 229 and 288 nm (log ε 4.48, 4.14) that coincide with the absorption characteristic for N-acetyl-2-aminoindoles [6]. The mass spectrum of this compound has an intense molecular ion peak of $[M]^+$ 242, which is in agreement with the value calculated for $C_{15}H_{18}N_2O$. There is an intense band at 1660 cm^{-1} (amide carbonyl) in the IR spectrum. The PMR spectrum in CCl_4 contains a doublet from the 3-CH_3 group (3H, 1.3 ppm), a singlet from the 10-CH_3 group (3H, 1.98 ppm), and a singlet from the CH_3CO protons (3H, 2.08 ppm), which corresponds to the assigned structure. In CF_3COOH, the signal of the 10-CH_3 group is split into a doublet with J = 6.8 Hz (1.51 ppm) as a consequence of protonation in the 10 position (X → XI); i.e., as in indoles themselves, the maximum electron density in these compounds is concentrated in the 3 position of the indole ring [8].

Scheme A

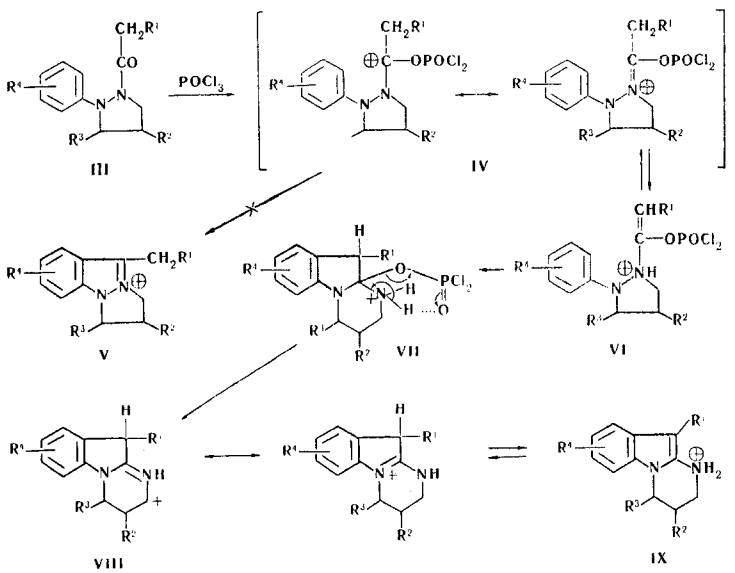
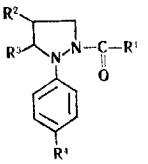
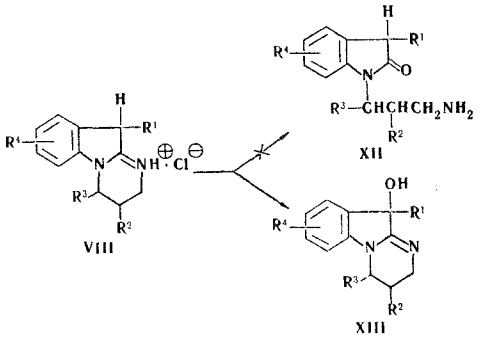


TABLE 1.

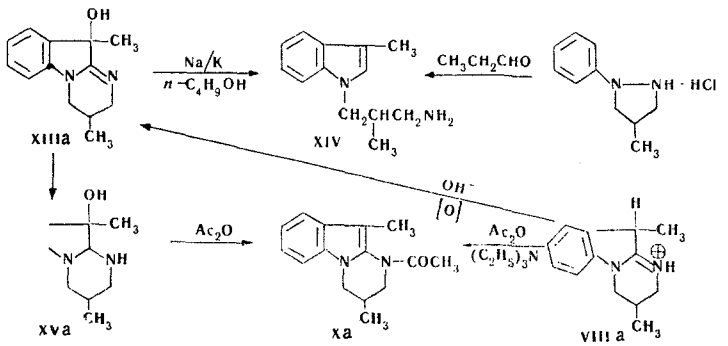


R¹	R²	R³	R⁴	Bp, °C (press., mm) (mp, °C)	Empirical formula	Found, %		Calc., %		Yield, %
						C	H	C	H	
C_2H_5	H	H	H	162—164 (7)	$C_{12}H_{16}N_2O$	70,36	7,61	70,59	7,85	54
C_2H_5	H	H	Br	(91—92)	$C_{12}H_{15}BrN_2O$	51,20	5,17	50,89	5,30	75
C_3H_7	H	H	H	172—173 (9)	$C_{13}H_{18}N_2O$	71,36	8,25	71,56	8,26	76
$(CH_3)_2CHCH_2$	H	H	H	168—169 (7)	$C_{14}H_{20}N_2O$	72,11	8,66	72,41	8,62	75
C_2H_5	CH_3	H	H	172—173 (9)	$C_{13}H_{18}N_2O$	71,32	8,54	71,56	8,26	75
C_2H_5	CH_3	H	Br	(41—43)	$C_{13}H_{17}BrN_2O$	52,81	5,54	52,52	5,72	64
n-C_3H_7	CH_3	H	H	173—175 (8)	$C_{14}H_{20}N_2O$	72,21	8,86	72,41	8,62	68
i-C_3H_7	CH_3	H	H	162—164 (7)	$C_{14}H_{20}N_2O$	72,36	8,78	72,41	8,62	74
$(CH_3)_2CHCH_2$	CH_3	H	H	169—171 (7)	$C_{15}H_{22}N_2O$	73,09	8,86	73,17	8,94	75
CF_3	CH_3	H	H	147—149 (7)	$C_{12}H_{13}F_3N_2O$	56,09	5,10	55,81	5,04	69
C_6H_5	CH_3	H	H	(122—124)	$C_{16}H_{18}N_2O$	75,72	7,21	75,58	7,08	65
C_2H_5	H	C_6H_5	H	(75—76)	$C_{18}H_{20}N_2O$	76,89	6,91	77,14	7,14	36

Only oxygen-containing compounds were obtained in attempts to isolate the bases from salts VIII under various conditions. It might have been assumed that rapid hydrolysis to XII would occur during alkalinization, but the mass spectra of the substances obtained contain intense M−15, M−17, and M−18 peaks, which correspond to cleavage of CH_3, OH, and H_2O, which is difficult to correlate with the possible disintegration of XII.



The reduction of XIIIa, formed from VIIIa ($R^1 = R^2 = CH_3$, $R^3 = R^4 = H$), by sodium−potassium alloy in butyl alcohol leads to aminoalkylindole XIV, which was obtained by alternative synthesis from 1-phenyl-4-methylpyrazolidine hydrochloride and propionaldehyde, as was done for other 1-(3-aminoalkyl)indoles [3]. The IR spectra of XIV synthesized by various routes were completely identical.



The IR spectrum of XIIIa in CCl_4 contains an absorption band at 3600 cm^{-1}, which corresponds to the stretching vibrations of the OH group, which does not appear when the spectra of concentrated solutions and of mineral oil suspensions are recorded, because of intermolecular hydrogen bonding. The absence of splitting of the signal of one methyl group and the presence of signals of all of the protons of the tetrahydropyrimidine ring in the PMR spectrum of a CF_3COOH solution corresponds to structure XIIIa (see Fig. 1).

The presence of a C = N bond is confirmed by the IR spectra, which contain the intense absorption at 1690-1710 cm^{-1} that is characteristic for 1,3,3-trisubstituted 2-iminoindolines [6], and also by the reduction of XIII to the corresponding hexahydropyrimidoindoles (XV) by lithium aluminum hydride. The absorption at 1690 cm^{-1} (C = N) vanishes in the IR spectra of XV, and NH vibrations appear at 3300 cm^{-1}. The mass spectrum of XVa contains an intense molecular ion peak of $[M]^+$ 218 and intense M−15, M−17, and M−18 peaks, which correspond to the primary act of disintegration with cleavage of CH_3, OH, and H_2O. The action of acetic anhydride on XVa leads to cleavage of water with simultaneous acetylation and the formation of Xa, which is identical to the compound obtained by the acetylation of VIIIa. The action of acids (for example CF_3COOH) on XVa also leads to the facile loss of a water molecule to form VIIIa, which is oxidized to XIIIa by alkalinization.

The entry of an OH group into the β-position of indole is not unique. There are data that indicate that indoles that contain alkoxy, alkylthioxy, or amino groups in the 2 position are oxidized at a higher or lower rate in air in alkaline media to give 3-hydroxy derivatives [9].

The cyclization to form tetrahydropyrimido[1,2-a]indoles is a general reaction and proceeds with various 1-aryl-2-acylpyrazolidines that contain substituents in both the phenyl and pyrazolidine rings. The structure of the acyl residue does not play a substantial role, but as is apparent from the scheme of the process, the presence of at least one hydrogen atom attached to the α-carbon atom of the acyl residue is absolutely necessary for the reaction. Thus 1-phenyl-2-trifluoroacetyl- or 2-benzoylpyrazolidines are recovered unchanged from the reaction mixture, even after prolonged refluxing with phosphorus oxychloride.

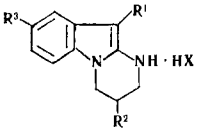
In addition to phosphorus oxychloride, PCl_3 and PBr_3 can also be used as the condensing agent, and the reaction rate increases markedly in the order $POCl_3 < PCl_3 < PBr_3$. Thus, while it is necessary to reflux the mixture in ether from 12 to 24 h for the complete conversion of IIIa ($R^1 = R^2 = CH_3$, $R^3 = R^4 = H$) to VIIIa, the reaction with PCl_3 proceeds in 1-2 h at room temperature, and the reaction with PBr_3 proceeds exothermically several minutes after mixing the reagents in absolute ether. The reaction is easily monitored by chromatography of the reaction mixture on aluminum oxide with elution by benzene−methanol (10:1). The end of the reaction is determined from the disappearance of the spot of the starting acylpyrazolidine with R_f 0.65-0.75 and the appearance of a new spot with R_f 0.15-0.35. The reaction products usually precipitate from the reaction mixture as HHal salts, but isolation is hindered in the case of the bromides because of their hygroscopicity.

The described reaction is a new transformation in the cyclic acylhydrazine series that leads to previously unknown tetrahydropyrimido[1,2-a]indoles.

EXPERIMENTAL

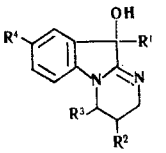
1-Aryl-2-acylpyrazolidines (III). A suspension of 0.2 mole of lithium aluminum hydride in 100 ml of absolute ether was added slowly to 0.1 mole of the appropriate 1-aryl-3-pyrazolidone in 200 ml of absolute ether, and the mixture was refluxed for 4-6 h and cooled. The excess lithium aluminum hydride was decomposed successively with 150 ml of moist ether and water. The inorganic precipitate was removed by filtration and washed three times with ether. The ether was removed by distillation, and the residue was dissolved in benzene. A molar excess of the appropriate acid anhydride was added, and the mixture was

TABLE 2.



R¹	R²	R³	Mp, °C	λmax (in methanol), nm		Empirical formula	Found, %		Calc., %		Yield %
				λmax, nm	(lg ε)		C	H	C	H	
CH_3	H	H	239—241	216; 264	4,25; 4,06	$C_{12}H_{14}N_2 \cdot HCl$	64,62	6,62	64,63	6,73	58
CH_3	CH_3	H	269—270	263; 266	4,09; 4,09	$C_{13}H_{16}N_2 \cdot HCl$	65,33	7,32	65,68	7,16	53
CH_3	CH_3	H	268—270	218; 265	4,21; 4,08	$C_{13}H_{16}N_2 \cdot HBr$	55,71	6,15	55,51	6,05	78
CH_3	CH_3	Br	287—288	214; 270	4,57; 4,32	$C_{13}H_{15}BrN_2 \cdot HCl$	49,09	5,22	49,51	5,08	61
C_2H_5	CH_3	H	205—206	218; 267	4,28; 3,91	$C_{14}H_{18}N_2 \cdot HCl$	66,96	7,60	67,06	7,57	56

TABLE 3.



R¹	R²	R³	R⁴	Mp, °C	λmax (in methanol), nm	lg ε	Empirical formula	Found, %		Calc., %		Yield %
								C	H	C	H	
CH_3	H	H	H	202—204	221; 266; 297	4,20; 4,10; 3,42	$C_{12}H_{14}N_2O$	71,24	7,13	71,38	6,94	70
CH_3	CH_3	H	H	228—230	220; 267; 298	4,22; 4,13; 3,44	$C_{13}H_{16}N_2O$	72,37	7,71	72,22	7,41	68
CH_3	H	C_6H_5	H	252—254	210; 268; 298	4,32; 4,21; 3,44	$C_{18}H_{18}N_2O$	77,57	6,80	77,75	6,48	59
CH_3	CH_3	H	Br	246—247	213; 276; 308	4,33; 4,19; 3,49	$C_{13}H_{15}BrN_2O$	53,06	5,35	52,86	5,09	67
C_2H_5	CH_3	H	H	210—212	266; 268; 297	4,11; 4,14; 3,44	$C_{14}H_{18}N_2O$	72,99	7,85	73,09	7,83	71

refluxed for 2 h. The benzene was removed by distillation, and the residue was vacuum distilled. When acid chlorides were used, the pyrazolidine was dissolved in dry benzene, an equimolar amount of diethylamine was added, and a solution of the acid chloride in benzene was added slowly with stirring to the mixture. The mixture was then washed successively with water and dilute alkali solution. The benzene solution was dried with potassium carbonate, the benzene was removed by distillation, and the residue was vacuum distilled. The physical constants and yields of the 1-aryl-2-acylpyrazolidines are presented in Table 1.

1,2,3,4-Tetrahydropyrimido[1,2-a]indoles (VIII). A mixture of 0.02 mole of the appropriate acylpyrazolidine and 0.06 mole of phosphorus oxychloride or phosphorus trichloride in 150 ml of absolute ether was allowed to stand at room temperature for 7-10 days or was refluxed for 12-24 h. The precipitate was removed by filtration, washed with absolute ether, dried in a vacuum desiccator, and recrystallized from propanol. In the preparation of the hydrobromides, PBr_3 was added to a solution of the acylpyrazolidine in absolute ether, and the mixture was allowed to stand for 1-2 h with periodic shaking. The resulting precipitate was treated as above. The physical constants and yields of the products are presented in Table 2.

3,10-Dimethyl-1-acetyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole (X). A mixture of excess acetic anhydride and triethylamine was added to 2.4 g (0.01 mole) of VIIIa ($R^1 = R^2 = CH_3$, $R^3 = R^4 = H$), and the mixture was heated at 90° for 1 h. The excess diethylamine was removed by distillation, and the residue was poured into water. The mixture was made alkaline to pH ~ 9 and extracted with ether. The extract was dried with potassium carbonate, the ether was removed by distillation, and the residue was vacuum distilled to give 1.8 g (75%) of a product with bp 205-208° (5 mm). UV spectrum in methanol: λ_{max} 229, 288 nm (log ε 4.48, 4.14). Found: C 74.64; H 7.39%. $C_{15}H_{18}N_2O$. Calculated: C 74.21; H 7.42%.

10-Hydroxy-2,3,4,10-tetrahydropyrimido[1,2-a]indoles. A 0.01-mole sample of tetrahydropyrimidoindole hydrochloride (see Table 2) was dissolved in water, and the solution was made alkaline to pH ~ 9. The product was extracted with ether or chloroform, the solvent was removed by distillation, and the residue was recrystallized from alcohol or aqueous alcohol. The physical constants and yields are presented in Table 3.

10-Hydroxy-3,10-dimethyl-1,2,3,4,10,10a-hexahydropyrimido[1,2-a]indole. A suspension of 1 g (0.026 mole) of lithium aluminum hydride in 50 ml of absolute tetrahydrofuran (THF) was added to a solution of 2.16 g (0.01 mole) of 10-hydroxy-3,10-dimethyl-2,3,4,10-tetrahydropyrimido[1,2-a]indole in 100 ml of absolute THF, and the mixture was refluxed for 6 h. The excess lithium aluminum hydride was decomposed with water, and the inorganic precipitate was removed by filtration and washed with ether. The organic layer was dried with sodium sulfate, the solvent was removed by distillation, and the residue was recrystallized from aqueous alcohol to give 1.52 g (70%) of a product with mp 186-187°. UV spectrum (in

methanol): λ_{max} 2.53, 300 nm (log ε 4.09, 3.42). Found: C 71.46; H 8.20%. $C_{13}H_{18}N_2O$. Calculated: C 71.56; H 8.26%.

1-(3-Amino-2-methylpropyl)-3-methylindole. A) A 1.7-g sample of sodium metal was fused with 0.5 g of potassium in absolute xylene, the mixture was cooled, and the xylene was decanted. A boiling solution of 2.16 g (0.01 mole) of 10-hydroxy-3,10-dimethyl-2,3,4,10-tetrahydropyrimido[1,2-a]indole in 100 ml of absolute n-butyl alcohol was added to the alloy. At the end of the reaction, 100 ml of H_2O was added to the reaction mass and the mixture was acidified to pH ~ 2. The n-butyl alcohol was removed by steam distillation, the mixture was made alkaline to pH ~ 9, and the 1-(3-amino-2-methylpropyl)-3-methylindole was distilled into dilute hydrochloric acid. The mixture was evaporated, and the hydrochloride was recrystallized from absolute alcohol to give 67% of a product with mp 203-204°. Found: C 65.38; H 7.92%. $C_{13}H_{18}N_2 \cdot HCl$. Calculated: C 65.49; H 7.98%.

B) A mixture of 1 g (0.005 mole) of 1-phenyl-4-methylpyrazolidine hydrochloride and 0.29 g (0.005 mole) of propionaldehyde was refluxed in absolute methanol for 4 h. The methanol was removed by distillation, and the residue was recrystallized from absolute alcohol to give 25% of a product with mp 203-204°. This product did not depress the melting point of the product obtained by method A.

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