REACTION OF 1-ACYL-2-PHENYLPYRAZOLIDINES WITH IMMINIUM SALTS

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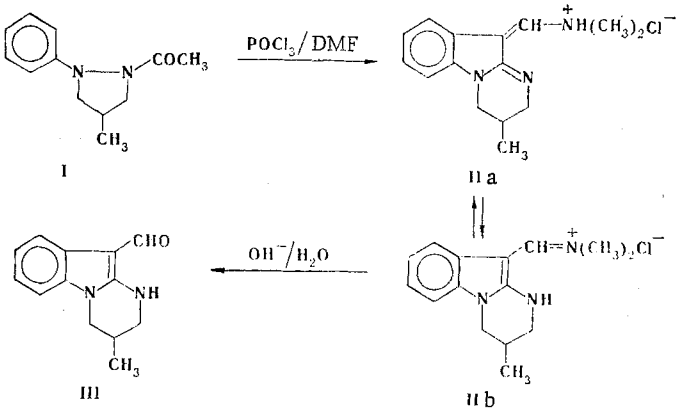
UDC 547.773'759.3'859.7:542.953:541.124:543.422

The reaction of 1-acetyl-2-phenyl-4-methylpyrazolidine with imminium salts leads to the formation of 3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]-10-methylenedimethylimminium chloride, the alkaline hydrolysis of which gives 3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]-10-aldehyde. Similar reactions with 1-propionyl and 1-phenylacetyl derivatives leads to nonformylated indolization products. The relative reactivities of the imminium were studied.

It has been shown by A. N. Kost [1-3] that the reaction of carboxylic acid arylhydrazides, as well as their cyclic analogs, viz., acylarylpyrazolidines, with reagents such as $POCl_3$, PCl_3, and PBr_3 leads to the formation of 2-aminoindole hydrochlorides or 1,2,3,4-tetrahydropyrimido[1,2-a]indoles, respectively. However, the cyclization of arylhydrazides of acetic acid and acetylarylpyrazolidines, which leads to 3-unsubstituted 2-aminoindoles, which are most promising in a synthetic respect, proceeds with great difficulty under these conditions [3].

It is known that acetic acid arylamides react readily with $POCl_3$—CMF (the Vilsmeier reagent) to give heterocyclic compounds [4, 5]. One might have expected that acetic acid arylhydrazides, particularly 1-acetylarylpyrazolidines, would also react just as readily with this complex.

We have carried out the reaction of 1-acetyl-2-phenyl-4-methylpyrazolidine (I) with an equimolar amount of the phosphorus oxychloride—dimethylformamide (DMF) complex in excess DMF.



3-Methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole-10-methylenedimethylimminium chloride (II) was isolated in quantitative yield in this case.

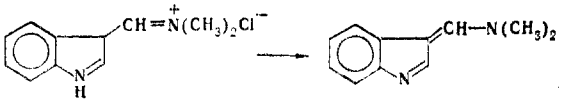
The PMR spectrum of II is similar in many respects to the spectrum of the 3-methyltetrahydropyrimidoindole hydrochloride formed from acetylphenylpyrazolidine I under the conditions of the Kost reaction [1]. Thus a doublet of the CH_3 group in the 3 position (3H, 1.1 ppm) and a multiplet of five protons of a tetrahydropyrimidine ring at 2.0-4.2 ppm are observed, and this constitutes evidence for retention of the cycloalkyl fragment of the starting acetylphenylpyrazolidine. The indole character of II is confirmed by the presence in the PMR spectrum of signals of four aromatic protons at 7.0-7.6 ppm; the signal of one of these pro-

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 397-401, March, 1983. Original article submitted October 10, 1982.

 0009-3122/83/1903-0324$07.50

tons is separated from the signals of the three remaining protons by 0.2 ppm, which corresponds to the similar pattern for the signal of the fourth proton in the PMR spectra of 2-acylindoles [6]. The weak-field singlet of one proton at 8.8 ppm corresponds to the methylidyne proton in the 10 position. The labile proton attached to the nitrogen atom in II appears in the form of a broad singlet at 10.1 ppm, and its acidic character is confirmed by the fact that this signal vanishes when deuteromethanol is added to a sample of this compound. A singlet of six protons of the dimethylamino group is observed at 3.5 ppm, and this makes it possible to assign structure IIa to II. Data from the IR spectra, in which an absorption band of a conjugated C=N bond at 1640 cm^{-1} and a broad absorption band of an amino group in the salt form at 2800-3000 cm^{-1} are observed, also constitute evidence in favor of this structure. The signal of the protons of the dimethylamino group is split into two singlets, which corresponds to structure IIb in which both methyl groups are rigidly fixed, when a solution of II in DMSO is heated to 70-80°C and after prolonged standing at room temperature. These data constitute evidence for the existence in solution of two tautomeric forms of II, which exist in equilibrium.

Dimethylimminium salts similar to II are formed as intermediates in the formylation of indole, pyrrole, and other heteroaromatic compounds under the conditions of the Vilsmeier–Haack reaction and can be isolated [7, 8]. Smith [7] has shown that the alkaline hydrolysis of 3-indolyldimethylimminium chloride (IV) leads to the formation of indole-3-aldehyde in quantitative yield; however, enamine V can be isolated under mild conditions (by neutralization with a dilute solution of alkali at 0°C).



IV V

The analogous bases of the pyrrole series can be isolated only under anhydrous conditions [8]. 3-Methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole-10-aldehyde (III) is formed in quantitative yield in the alkaline hydrolysis of II at both room temperature and under milder conditions. The PMR spectrum of this compound does not contain signals of the protons of the dimethylamino group, and the weak-field singlet of one proton at 9.8 ppm corresponds to an aldehyde proton. The proton attached to the nitrogen atom shows up in the form of a broad signal at 7.8 ppm. An absorption band of a carbonyl group at 1640 cm^{-1} is observed in the IR spectrum of III. This low value of the frequency of the vibrations of the C=O group, which is characteristic for 3-acylindoles, is explained by conjugation with the pyrrole fragment of the indole molecule [9]. The absorption band of an NH group appears at 3320 cm^{-1}, which corresponds to the absorption of the amino group in 2-aminoindoles formed in the Kost reaction [2].

The reaction of acetylphenylpyrazolidine I with chloromethylenedimethylimminium chloride $ClCH{=}N(CH_3)_2^+Cl^-$, which leads to II, proceeds just as readily as when $POCl_3$ in DMF is used. This confirms the fact that the reagent in this transformation is actually the imminium salt rather than $POCl_3$ as in the Kost reaction. It was found that a twofold amount of the imminium salt is required for a quantitative reaction, while only an equimolar amount of phosphorus oxychloride is sufficient. It may be assumed that the $HOPOCl_2$ residue formed in the reaction may react with the dimethylformamide, which is present in excess amounts, to give again the imminium salt, as is known to be the case for the incomplete esters of phosphorus oxychloride $ROPOCl_2$ and $(RO)_2POCl$ [10].

It is known that DMF forms imminium salts not only with $POCl_3$ but also with reagents such as p-tosyl chloride, benzoyl chloride, etc. [11-13]. We found that II is formed in the reaction of acetylphenylpyrazolidine I with p-tosyl chloride, benzoyl chloride, and triethyloxonium tetrafluoroborate in dimethylformamide, as well as when $POCl_3$ and chlorodimethylimminium chloride are used; however, in these cases the reaction proceeds under more severe conditions and gives the products in lower yields. The degree of conversion of the compound depends substantially on the structure of imminium salt $YCH{=}N(CH_3)_2^+X^-$ formed in the reaction (see Table 1). The reaction does not take place at all in the case of methylenedimethylimminium chloride (Y=H, X=Cl) – only starting acetylphenylpyrazolidine I was isolated after workup of the reaction mixture.

When we subjected acylphenylpyrazolidines that contain propionyl and phenylacetyl groups instead of an acetyl group to the reaction with the imminium salts we isolated saltlike com-

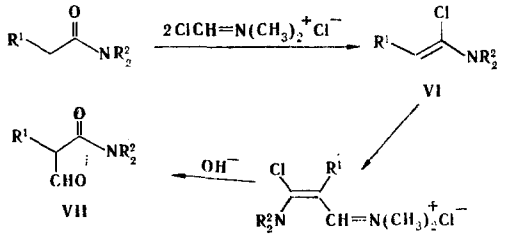
TABLE 1. Reaction of 1-Acetyl-2-phenyl-4-methylpyrazolidine with Imminium Salts $YCH=N(CH_3)_2^+X^-$ in Dimethylformamide

Reagent	Y	Reac. temp., °C	Heating time, h	Degree of conversion of I,* %
$POCl_3$	Cl	70—80	1	100
$ClCH=N(CH_3)_2^+Cl^-$	Cl	70—80	1	100
p-Tosyl chloride	OTs	100	5	74
PhCOCl	OCOPh	100	18	15
Et_3OBF_4	OEt	150	18	9
$CH_2=N(CH_3)_2^+Cl^-$	H	150	18	0

*The degree of conversion of I was determined from the yield of aminoindolealdehyde III after hydrolysis of the reaction mixture.

pounds, the alkaline hydrolysis of which leads to tetrahydropyrimido[1,2-a]-10-hydroxy-10-methyl(phenyl)indoles. These compounds are obtained by alkalization of solutions of the tetrahydropyrimidoindole hydrochlorides formed in the Kost reaction from the corresponding acylphenylpyrazolidines [2].

It is known [1] that the formation of enehydrazines is assumed to be the step that precedes indolization in the reaction of arylhydrazides with phosphorus oxychloride (the Kost reaction). Chloroenamines VI, which can react with a second molecule of the imminium salt to give α-formylated VII, are similarly formed in the reaction of carboxylic acid amides.



The transformation that we observed can evidently proceed via the scheme proposed for the Kost reaction with subsequent formylation of the resulting tetrahydropyrimidoindole. An alternative pathway includes formylation of a chloroenehydrazine of the VI type (as in the reaction of amides), which precedes indolization. Our data do not make it possible to choose in favor of one or the other sequence of formylation and indolization processes. Further research will be devoted to the study of this problem.

EXPERIMENTAL

The course of the reaction and the purity of the compounds obtained were monitored by thin-layer chromatography (TLC) on activity II aluminum oxide in a benzene—methanol system (10:1). The IR spectra of suspensions of the compounds in mineral oil or hexachlorobutadiene were recorded with a UR-20 spectrometer. The PMR spectra of solutions in $CDCl_3$ and d_6-DMSO were recorded with Varian T-60 and Tesla BS-497 spectrometers with an operating frequency of 100 MHz with tetramethylsilane as the internal standard.

3-Methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole-10-methylenedimethylimminium Chloride (II). A) A 0.46-ml (5 mmole) sample of $POCl_3$ was added with cooling to 5 ml of dry DMF, and the resulting solution was allowed to stand at room temperature for 30 min. A solution of 1.02 g (5 mmole) of 1-acetyl-2-phenyl-4-methylpyrazolidine in 5 ml of DMF was added, and the reaction mixture was heated at 70-80°C for 1 h. It was then cooled with a mixture of ice and salt, and the precipitated crystals were removed by filtration and washed with minimum amount of dry DMF and absolute ether to give 1.1 g (78%) of a product with mp 257°C (dec.). IR spectrum: 1640 (C=N) and 2800-3000 cm^{-1} (N—H). PMR spectrum (d_6-DMSO): 1.1 (3H, d, 3-CH_3, J = 7 Hz), 2.05-2.45 (1H, m, 3-H), 3.5 (6H, s, NMe_2), 2.7-4.2 (4H, m, 2-H, and 4-H), 7.0-7.35 (3H, m, 6-H, 7-H, 8-H), 7.45-7.65 (1H, m, 9-H), 8.85 (1H, s, CH=NMe_2), and 10.1 ppm (1H, broad, NH).

The reactions with p-tosyl chloride, benzoyl chloride, and triethyloxonium tetrafluoroborate were carried out similarly (see Table 1).

B) A 0.7-ml (10 mmole) sample of $SOCl_2$ was added carefully to 0.75 ml (10 mmole) of dry DMF, and the mixture was allowed to stand for 30 min. It was then heated to 40-45°C, and the liberated SO_2 was removed *in vacuo*. The resulting chloromethylenedimethylimminium chloride was dissolved in 5 ml of dry DMF, a solution of 1.02 g of acetylphenylpyrazolidine in 3 ml of DMF was added, and the reaction mixture was then worked up as in method A.

3-Methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole-10-aldehyde (III). A 0.5-g sample of II was dissolved in 10 ml of water, the solution was made alkaline to pH 11 with KOH solution, and the resulting precipitate was removed by filtration, washed with water, and recrystallized from benzene to give 0.4 g (98%) of a product with mp 225-226°C. IR spectrum: 1640 (C=O) and 3320 cm^{-1} (NH). PMR spectrum (in $CDCl_3$): 1.1 (3H, d, 3-CH_3, J = 7 Hz), 2.2-2.5 (1H, m, 3-H), 3.0-4.2 (4H, m, 2-H and 4-H), 7.0-7.6 (4H, m, 6-H, 7-H, 8-H, 9-H), 7.8 (1H, broad, NH), and 9.8 ppm (1H, s, CHO). Found: C 72.9; H 6.7%. $C_{13}H_{14}N_2O$. Calculated: C 72.9, H 6.5%.

10-Hydroxy-3,10-dimethyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole. A solution of 10 mmole of chloromethylenedimethylimminium chloride in 5 ml of DMF was added to a solution of 1.09 g (5 mole) of 1-propionyl-2-phenyl-4-methylpyrazolidine in 5 ml of dry DMF, and the mixture was heated at 70-80°C for 1 h. It was then cooled and poured into 30 ml of cold water, and the mixture was made alkaline to pH 11 with KOH solution and extracted with benzene. The combined benzene extracts were dried with anhydrous sodium sulfate, the benzene was evaporated, and the residue was recrystallized from benzene to give 0.36 g (32%) of a product with mp 227°C (mp 228-230°C [2]).

No melting-point depression was observed for a mixture of this product with a genuine sample. The IR spectra of the compound obtained and a genuine sample were identical.

10-Hydroxy-3-methyl-10-phenyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole. This compound, with mp 250°C (from benzene) (mp 252-254°C (from alcohol) [2]), was similarly obtained in 46% yield from 1-phenylacetyl-2-phenyl-4-methylpyrazolidine. The IR spectra of the compound obtained and a genuine sample were identical.

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