REACTION OF PHENYLHYDRAZIDES OF N-ACYL-β-PHENYL-β-ALANINE WITH PHOSPHORUS OXYCHLORIDE

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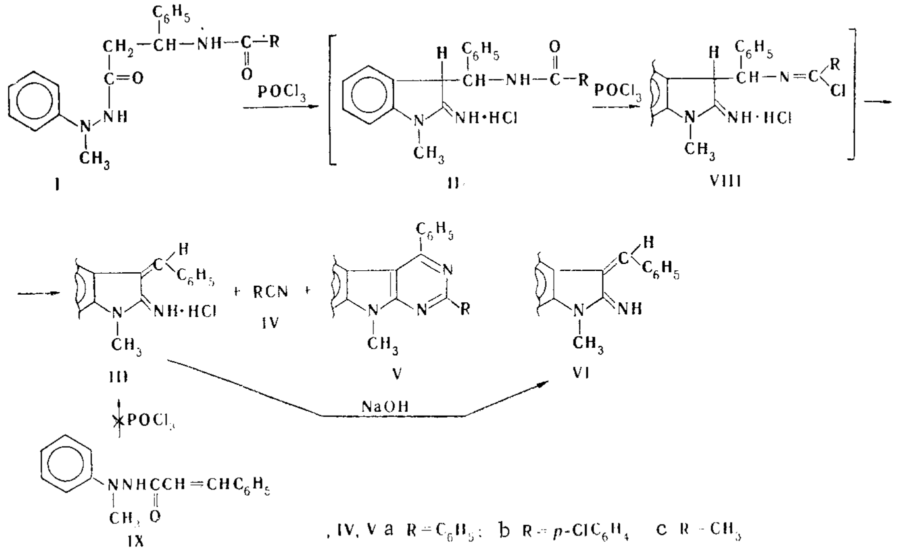
The reaction of N'-methyl-N'-phenylhydrazides of N-acyl-β-phenyl-β-alanine with phosphorus oxychloride is accompanied by cleavage of the C—N bond in the intermediately formed 2-aminoindole derivative and, after splitting out of an amide fragment, leads to 1-methyl-3-benzylidene-2-iminoindoline and nitriles. Pyrimido[4,5-b]indoles — products of cyclization of the corresponding intermediate 2-aminoindole derivatives — were isolated from the reaction mixtures in low yields. The structure of 1-methyl-3-benzylidene-2-iminoindoline was proved by alternative synthesis.

The reaction of N-phthalyl-β-alanine N'-methyl-N'-phenylhydrazide with phosphorus oxychloride leads to the corresponding 3-(ω-phthalimidomethyl)-2-aminoindole [1]. We have established in the present research that β-phenyl-β-alanine phenylhydrazides with an N-acetyl, N-benzoyl, or substituted N-benzoyl group react in a different way. After carrying out the rearrangement of hydrazides Ia-c under the usual conditions for this reaction, we isolated three substances instead of the expected reaction products (III). We assigned benzylidene derivative structure III to the principal reaction product, which is formed in all cases regardless of the hydrazide used. Broad absorption bands at 2200-3350 cm^{-1}, which correspond to the absorption of a saltlike amino group, and absorption bands at 1640 and 1680 cm^{-1}, which correspond to the absorption bands of C=C and C=N bonds, respectively, are present in the IR spectrum of III. A singlet of an N—CH$_3$ group at 3.52 ppm (3H) and an unresolved multiplet of nine aromatic protons at 7.8-8.0 ppm are observed in the PMR spectrum of a solution in D$_2$O. A molecular-ion peak with M$^+$ 234, which corresponds to the value calculated for this compound, is observed in the mass spectrum of free base VI, which was isolated from III, and its subsequent fragmentation does not contradict structure VI.



IV, V a R=C$_6$H$_5$; b R=p-ClC$_6$H$_4$, c R=CH$_3$

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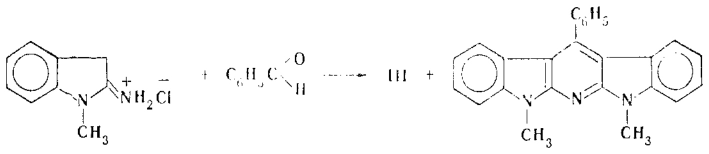
To completely confirm the structure of III we realized its alternative synthesis by condensation of 2-amino-1-methylindole hydrochloride with benzaldehyde via a known scheme [2]:



VII

In this case primarily diindolo[2,3-b;3',2'-e]pyridine VII is formed in addition to III under the reaction conditions.

The secondary reaction products are nitriles IVa-c. After rearrangement of hydrazide Ib, the corresponding nitrile IVb was isolated in an equimolar amount relative to benzylidene derivative III. The structure of nitrile IVb was proved by the complete agreement between its constants and the literature data for p-chlorobenzonitrile and the agreement between the IR, PMR, and mass spectra and the spectra of a genuine sample. The presence of benzonitrile and acetonitrile in the reaction mixtures after the rearrangements of hydrazides Ia, c was proved by gas—liquid chromatography (GLC). We assigned a pyrimidoindole structure (Va-c) to the third reaction product, which was isolated in very low yield. The structures of these compounds are confirmed by the spectral data. Thus the mass spectrum of Vc contains a molecular-ion peak with M^+ 273 (67%), which corresponds to the value calculated for this compound. The maximum peak in the mass spectrum is the M—1 peak (100%); this is characteristic for aromatic compounds that have a phenyl group in the α position relative to the nitrogen atom. The virtual absence of other fragment ions in the mass spectrum, except for doubly charged ions with m/e 135.5 (6.5%) and 136 (7.1%), constitutes evidence for the stability of Vc with respect to electron impact and for its high degree of aromatic character. A singlet of a methyl group at 2.57 ppm (3H), a singlet of an $N-CH_3$ group at 3.60 ppm (3H), and a multiplet of aromatic protons at 6.7-7.0 ppm (9H) are observed in the PMR spectrum of Vc. The formation of III-V can be explained if it is assumed that the rearrangement of phenylhydrazides Ia-c under the influence of $POCl_3$ under the selected conditions proceeds through the "normal" reaction product, viz., a 2-iminoindoline of the II type or its imidoyl chloride VIII.

The indicated intermediates, which have a labile hydrogen atom in the 3 position, can readily split out the corresponding amide or chloro imine to give benzylidene derivative III and subsequently nitriles IVa-c. If one assumes that splitting out of an amide occurs via cleavage of the C—N bond even in the starting hydrazide (Ia-c), cinnamic acid hydrazide should undergo further transformation. We synthesized this hydrazide (IX) and established that it is not converted to 3-benzylidene-2-iminoindoline (III) under the usual conditions of the rearrangement and is isolated unchanged from the reaction mixture.

The isolation of pyrimidoindoles V serves as an additional confirmation of the existence of II or VII as intermediates in the rearrangement of hydrazides I. Pyrimidoindoles V can be formed only as a result of intramolecular cyclization of II or VII with subsequent dehydrogenation, possibly due to oxidation by air oxygen.

Thus the transformation that we described in this paper confirms the definite sensitivity of the rearrangement of phenylhydrazides to structural factors in the acyl residue.

EXPERIMENTAL

The UV spectra of solutions of the compounds in alcohol were recorded with a Perkin-Elmer 402 spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with a Perkin-Elmer 577 spectrometer. The PMR spectra were recorded with a Tesla BS-467 spectrometer. The mass spectra were obtained with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing voltage of 70 eV. The course of the reactions was monitored by chromatography on activity II Al_2O_3 in a benzene—methanol system (10:1).

Cinnamic Acid N-Methyl-N-phenylhhydrzide (IX). A 16.65-g (0.1 mole) sample of cinnamoyl chloride was added slowly with stirring and cooling to a mixture of 12.2 ml (0.1 mole) of α-methyl-α-phenylhydrazine and 13.8 ml (0.1 mole) of triethylamine in 50 ml of absolute

TABLE 1. Characteristics of N'-Methyl-N'-phenylhydrazides Ia-c

Compound	mp, °C (ethanol)	IR spectrum, cm^{-1}	Found, %			Emperical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
Ia	206—208	1630, 1660, 3260	67,1	5,5	10,7	$C_{23}H_{22}N_3O_2Cl$	67,7	5,4	10,3	59
Ib	187—188	1635, 1668, 3260	73,7	6,4	11,6	$C_{23}H_{23}N_3O_2$	73,9	6,2	11,3	60
Ic	170—172	1600, 1660, 3280	69,1	6,7	13,6	$C_{18}H_{21}N_3O_2$	69,4	6,8	13,5	56

benzene, and the mixture was stirred for 2 h. The precipitate was removed by filtration, washed with water, and recrystallized from benzene to give 12.5 g (50%) of hydrazide IX with mp 125°C. IR spectrum: 1620 (C=C), 1655 (C=O), and 3170 cm^{-1} (NH). Found: C 76.6; H 6.7; N 11.2%. $C_{16}H_{16}N_2O$. Calculated: C 76.2; H 6.4; N 11.1%.

Hydrazides Ia-c were similarly obtained. The constants and yields of the hydrazides obtained are presented in Table 1.

Rearrangement of N-(p-Chlorobenzoyl)-β-phenyl-β-alanine N'-Methyl-N'-phenylhydrazide (Ib). A mixture of 2 g (5 mmole) of hydrazide Ib and 0.88 ml (10 mmole) of phosphorus oxychloride in 50 ml of absolute methylene chloride was refluxed for 60 h, after which the solvent and excess phosphorus oxychloride were evaporated, and absolute ether was added to the residue. The ether mixture was cooled, and the resulting crystals were removed by filtration, washed thoroughly with ether, and recrystallized from absolute alcohol to give 1 g (72%) of 1-methyl-2-benzylidene-2-iminoindoline hydrochloride (III) with mp 240°C (decomp.). Found: C 70.4; H 5.9; N 10.1%. $C_{16}H_{14}N_2 \cdot HCl$. Calculated: C 70.9; H 5.6; N 10.4%. Evaporation of the ether solution and recrystallization of the residue from alcohol gave 0.5 g of p-chlorobenzonitrile with mp 92-94°C (mp 92°C [3]). The alcohol solution remaining after recrystallization of hydrochloride III was evaporated, and the residue was transferred to a column filled with Al_2O_3 and eluted with benzene to give 0.04 g (2%) of 9-methyl-4-phenyl-2-(p-chlorophenyl)[4,5-b]pyrimidoindole (Vb) with mp 171-172°C. IR spectrum: 1590, 1620 cm^{-1}. Found: M 369 (371) (by mass spectrometry). $C_{23}H_{16}ClN_3$. Calculated: M 369.5.

Rearrangement of N-Benzoyl-β-phenyl-β-alanine N'-Methyl-N'-phenylhydrazide (Ia). A mixture of 0.75 g (2 mmole) of hydrazide Ia and 0.36 ml (4 mmole) of phosphorus oxychloride in 50 ml of absolute benzene was refluxed for 20 h, after which the benzene was removed by distillation, and 4 ml of ether was added to the residue. The precipitated crystals were removed by filtration to give 0.38 g (70%) of III with mp 240°C (from alcohol). The IR spectrum was identical to the spectrum of III obtained by rearrangement of hydrazide Ib. The alcohol filtrate was evaporated, and the residue was transferred to a column filled with Al_2O_3 and eluted with benzene to give 0.015 g (2%) of Va with mp 185°C (from alcohol). IR spectrum: 1595, 1610 cm^{-1}. Found: C 82.2; H 5.4; N 12.1%; M 335 (by mass spectrometry). $C_{23}H_{17}N_3$. Calculated: C 82.4; H 5.1; N 12.5%; M 335. The ether solution was washed with water and dried with $MgSO_4$. Benzonitrile was detected in the solution by GLC.

Rearrangement of N-Acetyl-β-phenyl-β-alanine N'-Methyl-N'-phenylhydrazide (Ic). A 0.29-ml (3.2 mmole) sample of phosphorus oxychloride was added to 0.5 g (1.6 mmole) of hydrazide Ic in 20 ml of absolute methylene chloride, and the mixture was refluxed for 50 h. The solvent and excess phosphorus oxychloride were evaporated, absolute ether was added to the oily residue, and the mixture was cooled, The resulting crystals were removed by filtration, washed with ether, and recrystallized from alcohol to give 0.26 g (60%) of III with mp 240°C (decomp.). The IR spectrum of this product was identical to the spectrum of the substance obtained by rearrangement of hydrazides Ia, b. The alcohol and ether filtrates were combined and evaporated, and the residue was transferred to a column filled with Al_2O_3 and eluted with benzene to give 0.045 g (10%) of Vc with mp 157-159°C (from alcohol). Found: C 79.1; H 5.5; N 14.9%; M 273 (by mass spectrometry). $C_{18}H_{15}N_3$. Calculated: C 79.2; H 5.5; N 15.3%.

Reaction of Cinnamic Acid N-Methyl-N-phenylhydrazide (IX) with Phosphorus Oxychloride. A mixture of 1.26 g (5 mmole) of hydrazide IX and 0.92 ml (10 mmole) of phosphorus oxychloride was refluxed for 60 h, after which the solvent and excess phosphorus oxychloride were evaporated, and the residue was recrystallized from benzene to give 1.1 g (85%) of starting hydrazide IX.

Condensation of 2-Amino-1-methylindole Hydrochloride with Benzaldehyde. A 0.2-ml (2 mmole) sample of benzaldehyde was added to a hot solution of 0.28 g (2 mmole) of 2-amino-1-

methylindole hydrochloride in 5 ml of absolute alcohol, and the mixture was refluxed for 3 h. It was then cooled and filtered to give 0.1 g (30%) of diindolo[2,3-b;3',2'-e]pyridine (VII) with mp 290°C (from benzene) (mp 288-290°C [4]). The filtrate was evaporated, absolute ether was added to the residue, and the mixture was filtered to give 0.045 g (9%) of hydrochloride III.

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VINYLOGOUS ANHYDRO BASES OF PYRIDYLINDOLES

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The reaction of quaternary salts of pyridylindoles, the heterocyclic rings in which are separated by an ethylene grouping, with alkali was investigated. It was established that 2-(3-indolylvinyl)pyridinium and -quinolinium salts are converted to stable colored anhydro bases in a methanol solution of alkali.

The reaction of quaternary salts of pyridylindoles with alkali leads to stable colored anhydro bases [1, 2]. The anhydro bases of pyridylindoles proved to be extremely reactive compounds and extremely interesting subjects for diverse physicochemical studies.

In the present research we investigated the reaction of quaternary salts of pyridylindoles, the heterocyclic rings of which are separated by a vinyl grouping, with alkali. The possibility of the synthesis of anhydro bases from 2-(3-indolylvinyl)pyridine methiodide is mentioned in the literature [3], but no information regarding the reactivity and physicochemical properties of this compound is available. However, the study of the similarly constructed quaternary salts of sterically hindered p-hydroxystyrylpyridines in alkaline media has been limited to only their acid—base transformations [4].

2-(3-Indolylvinyl)pyridinium salts (I, II) are converted to the deeply colored anhydro bases (III, IV) in a methanol solution of alkali. The presence of a powerful chromophore in the form of a system of conjugated bonds makes their color considerably deeper as compared with the anhydro bases of pyridylindoles (407 and 530-550 nm, respectively) (see next page for scheme). Only deprotonation occurs when quaternary salts I and II are treated with alkali. The products of possible competitive dealkylation of the pyridine ring cannot be detected in even trace amounts. The same pattern was also observed in the synthesis of anhydro bases from quaternary salts of pyridylindoles [1, 2]. Quantum-chemical calculations [by the Pariser—Parr—Pople (PPP) method] show that the highest positive π-electron charge is concentrated on the indole nitrogen atom, which also determines the direction of nucleophilic attack by the hydroxide ion on the N—H group of the indole ring [1]. The presence of a vinyl grouping separating the heterocyclic rings does not change the electron balance of the cation or consequently, the direction of attack by the hydroxide ion. 2-(3-Indolylvinyl)quinoline methiodide (V) — a vinylog of 2-(3-indolyl)quinoline, the behavior of which under alkaline conditions differs somewhat from the behavior of V — reacts similarly with hydroxide ion. In fact, a small amount of dealkylation product is also formed along with the anhydro base in the reaction of 2-(3-indolyl)quinoline with alkali [2].

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