SYNTHESIS OF 3,3-DISUBSTITUTED 2-IMINOINDOLINES BY CYCLIZATION OF 1-PHENYL-2-ACYLHYDRAZINES

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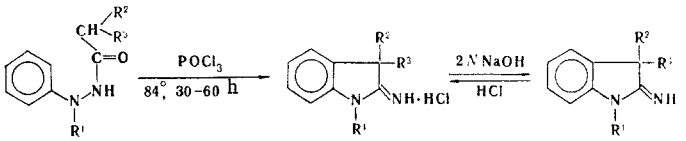
3,3-Disubstituted 2-iminoindolines and the corresponding 10,10-disubstituted tetrahydropyrimido-[1,2-a]indoles, including compounds with spiran structures, were synthesized by reaction of 1-phenyl-2-acylhydrazines and 1-phenyl-2-acylpyrazolidines geminally substituted at the α-carbon atom of the acyl residue with phosphorus oxychloride. An instance of cleavage of the methyl group was detected.

2-Aminoindoles are formed by rearrangement of 1-aryl-2-acylhydrazines under the influence of phosphorus halides [1]. All of the described examples involve hydrazides with an α-methylene group in the acyl residue. In the case of branching at the α-carbon atom one might expect steric hindrance or even migration of one of the groups. We therefore synthesized a number of 1-phenyl-2-acylhydrazines (I) with a methylidyne grouping in the α position.

It was found that I reacts with phosphorus oxychloride in benzene (or ether) to give 3,3-disubstituted 2-iminoindolines (II) in good yields:



I II III

I, II, III a $R^1=R^2=R^3=CH_3$; b $R^1=R^2=CH_3$, $R^3=C_6H_5$; c $R^1=CH_2C_6H_5$, $R^2=R^3=CH_3$; d $R^1=CH_3$, $R^2+R^3=(CH_2)_5$

The UV spectrum of iminoindoline IIa in alcohol has characteristic (for iminoindolines [1, 2]) absorption maxima at 214 and 262 nm (log ε 4.28 and 4.10), and an intense absorption band at 1700 cm^{-1} and a broad absorption band at 2600-3200 cm^{-1}, which corresponds to a protonated amidine structure, are observed in its IR spectrum. The PMR spectrum (in CF_3COOH) has a singlet of two methyl groups in the 3 position (1.21 ppm, 6H), a singlet of an N–CH_3 group (3.28 ppm, 3H), a multiplet of aromatic protons (4H), and a broad doublet of a hydrogen atom attached to a nitrogen atom centered at 7.5 ppm (2H). The presence of this doublet constitutes evidence that the double bond is localized between the α-carbon atom and the exocyclic nitrogen atom and that protonation of II takes place at this nitrogen atom. The PMR spectrum of base IIIa (in CCl_4) contains the same signals, but there is a broad signal of only one NH proton at 7.1 ppm. Similar spectra were obtained for the other compounds (II and III).

The rearrangement also took place successfully with cyclohexanecarboxylic acid hydrazide, which forms 3-spiroindoline IId. The structure of the latter is confirmed by the characteristic IR and UV spectra. A doublet of cyclohexane ring protons centered at 1.27 ppm (10H, J = 6 Hz), an N–CH_3 signal (2.7 ppm, 3H), and a multiplet of four aromatic protons (6.2-7.3 ppm) are observed in the PMR spectrum of base IIId (in CD_3OD). Thus migration or splitting out of alkyl groups from the 3 position does not occur during rearrangement of I to 2-iminoindolines II.

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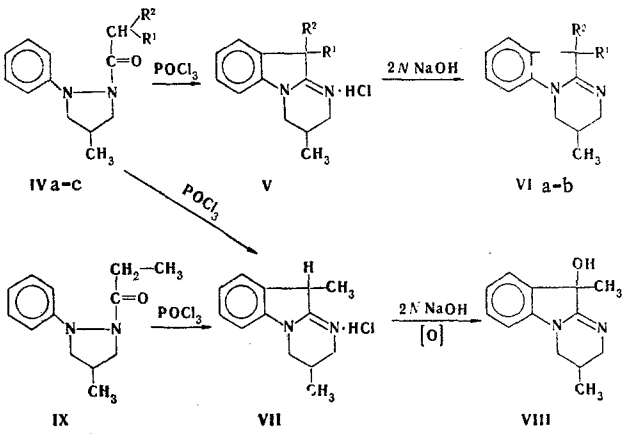
It must be noted that, according to the results of elementary analysis, all of the II obtained immediately after the rearrangement, even after repeated crystallization, contain considerable amounts of phosphorus (sometimes up to 5%). However, we were unable to isolate individual phosphorylated compounds, whereas the data from the IR spectra (stretching vibrations of an ammonium group) and PMR spectra (signals of the protons of a NH_2 group) make it possible to suppose that the formation of a covalent P–N bond does not occur to a significant degree in this case. Compounds II apparently contain a difficult-to-separate admixture of phosphoric acid salts of indoline III. The reaction products were purified by conversion to bases III, from which the individual hydrochlorides (II) were obtained by treatment with hydrogen chloride.

Bases III were obtained as difficult-to-crystallize oils that are stable in air; this distinguishes them from 3-monoalkyl-2-aminoindoles, which are rapidly converted to 3-hydroxy or 3-peroxy compounds in air [1, 3]. This difference is a confirmation of the fact that migration of one of the gem-dialkyl groups, as is observed in the Planchet, rearrangement [4], does not occur on protonation of bases III or during cyclization to salts II.

Cyclic analogs of arylhydrazines, i.e., 1-phenyl-2-acylpyrazolidines (IV), also undergo the described reaction to give the corresponding pyrimido[1,2-a]indoles (V).



IV, VI a $R^1=CH_3$, $R^2=C_6H_5$; b $R^1+R^2=(CH_2)_5$; IV c $R^1=R^2=CH_3$

The structures of V and VI are confirmed by their characteristic IR, UV, and PMR spectra. An intense molecular ion peak with M^+ 276 (calculated value 276) is observed in the mass spectrum of VIa; the subsequent fragmentation corresponds to the structure proposed for this compound.

It should be noted that, in contrast to noncyclic phenylacylhydrazines I, products of the elimination of alkyl groups are detected chromatographically along with VI in the reaction of IV with phosphorus oxychloride. This sort of elimination occurs only to a very small degree in the case of IVa, b, whereas it predominates in the case of IVc, and compounds of the V type cannot be isolated in this case. The product of the reaction of IVc with $POCl_3$ was salt VII, after alkalization of which oxidation product VIII was isolated; the physical constants of VIII and its IR and PMR spectra proved to be identical to those of a sample obtained from the corresponding propionylpyrazolidine IX.

Thus the investigated reaction is a convenient method for the synthesis of 3,3-disubstituted 2-iminoindolines as well as some 10,10-disubstituted 2,3,4,10-tetrahydropyrimido[1,2-a]indoles, including compounds with spiran structures.

EXPERIMENTAL

The UV spectra of alcohol solutions of the compounds were recorded with a Specord spectrophotometer. The IR spectra of mineral oil suspensions (hexachlorobutadiene suspensions at 2000-3400 cm^{-1}) of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of trifluoroacetic acid solutions of the compounds were obtained with a Varian T-60 spectrometer with hexamethyldisiloxane as the external standard. The mass spectra were recorded with an MKh-1303 spectrometer with a modified inlet into the ion source. The reactions and the purities of the compounds obtained were monitored by chromatography on aluminum oxide in a benzene–methanol system (20:1).

1,3,3-Trimethyl-2-iminoindoline Hydrochloride (IIa). A mixture of 2 g (0.01 mole) of 1-methyl-1-phenyl-2-isobutyrylhydrazine (Ia) and 4.6 g (0.03 mole) of phosphorus oxychloride in 75 ml of absolute benzene was

refluxed for 24 h, after which the resulting precipitate was removed by filtration, washed with absolute ether, and dried in a vacuum desiccator. Recrystallization from absolute alcohol gave 1.7 g of a substance with mp 210-212° (dec.). A 0.8-g sample of this product was dissolved by heating in water, and the resulting solution was cooled, made alkaline to pH ~9, and extracted thoroughly with ether. The extract was dried with potassium carbonate, the ether was removed by distillation to a volume of ~15 ml, and the concentrated solution was treated with an ether solution of HCl until it gave an acid reaction. The liberated oil was washed out with absolute ether, absolute alcohol was added to the ether to completely dissolve the oil, and the solution was allowed to stand in a desiccator. The resulting precipitate was removed by filtration and recrystallized from alcohol–ether to give 0.6 g (63% based on Ia) of IIa with mp 257°. Found %: C 62.6; H 7.2. $C_{11}H_{14}N_2 \cdot HCl$. Calculated %: C 62.5; H 7.1.

3,3-Dimethyl-1-benzyl-2-iminoindoline Hydrochloride (IIc). A mixture of 3.2 g (0.012 mole) of 1-benzyl-1-phenyl-2-isobutylhydrazine (Ic) and 3.68 g (0.024 mole) of phosphorus oxychloride was refluxed in absolute benzene for 20 h, after which water was added, and the mixture was allowed to stand for 4 h with periodic stirring. The benzene solution was separated, and the residue was heated in water until it dissolved completely. The solution was cooled, made alkaline to pH ~9, and extracted with ether. The mixture was then worked up as in the case of IIa to give 1.3 g (38%) of a product with mp 277-280° (from absolute alcohol). UV spectrum: λ_{max} 209 and 260 nm (log ε 4.24 and 3.64). PMR spectrum, δ, ppm: 1.53 (s, two β-CH_3 groups), 5.13 (s, N-CH_2), 7.01-7.40 (m, 9H aromatic), 7.70 (s, NH), and 8.06 (s, NH). Found %: C 71.0; H 6.7. $C_{17}H_{18}N_2 \cdot HCl$. Calculated %: C 71.4; H 6.6.

1-Methyl-3,3-pentamethylene-2-iminoindoline (IIId). A mixture of 2.3 g (0.01 mole) of cyclohexanecarboxylic acid β-methyl-β-phenylhydrazide (Id) and 3.1 g (0.02 mole) of phosphorus oxychloride was refluxed in 50 ml of absolute benzene for 10 h, after which the resulting precipitate was removed by filtration, washed with ether, and recrystallized from aqueous alcohol to give 1.8 g of a product with mp ~300° (dec.). The product was dissolved in boiling water, and the solution was made alkaline to pH ~9 and extracted with ether. The extract was dried with K_2CO_3, the ether was removed by distillation, and the residual oil began to crystallize on standing to give 1.1 g (51%) of a product with mp 48°. Found %: C 78.5; H 8.5; N 13.0; M 214 (by mass spectrometry) $C_{14}H_{18}N_2$. Calculated %: C 78.5; H 8.4; N 13.1; M 214.

1,3-Dimethyl-3-phenyl-2-iminoindoline Hydrochloride (IIb). The method used to obtain IIc was used to obtain this compound from 2.5 g (0.02 mole) of hydratropic acid β-methyl-β-phenylhydrazine (Ib) and 3 g (0.02 mole) of phosphorus oxychloride. The yield of product with mp 282-290° was 1.3 g (48%). UV spectrum: λ_{max} 262 nm (log ε 3.85). IR spectrum: 1700 cm^{-1} (C=N). PMR spectrum, δ, ppm: 1.79 (s, β-CH_3), 3.64 (s, N-CH_3), and 6.85-7.85 (m, 9H aromatic). Found %: C 70.1; H 6.3. $C_{17}H_{16}N_2 \cdot HCl$. Calculated %: C 70.4; H 6.2.

3,10-Dimethyl-10-phenyl-2,3,4,10-tetrahydropyrimido[1,2-a]indole Hydrochloride (Va). A 3.1-g sample of dry triethylamine was added to a solution of 4.9 g (0.03 mole) of distilled 4-methyl-1-phenylpyrazolidine [5] in 50 ml of absolute benzene, after which a solution of 5.5 g (0.03 mole) of hydratropoyl chloride in 50 ml of absolute benzene was added slowly with stirring. At the end of the addition, the mixture was stirred at room temperature for 1 h, after which 100 ml of water was added. The benzene solution was separated, washed successively with water, saturated $NaHCO_3$ solution, and water, and dried with K_2CO_3. The benzene was removed by distillation, and 100 ml of absolute benzene and 7 g (0.045 mole) of phosphorus oxychloride were added to the residual light-yellow oil (7.8 g) without further purification, and the mixture was refluxed for 48 h. The resulting precipitate was removed by filtration and worked up as in the case of IIId. Found % for base VIa: C 83.0; H 7.4; Mol. wt. 276 (by mass spectrometry). $C_{19}H_{20}N_2$. Calculated %: C 82.6; H 7.3; Mol. wt. 276.

The hydrochloride [4.6 g (49% based on the starting pyrazolidine)] had mp 250° (from absolute alcohol). Found %: C 73.1; H 6.9. $C_{19}H_{20}N_2 \cdot HCl$. Calculated %: C 73.0; H 6.7.

3-Methyl-10,10-pentamethylene-2,3,4,10-tetrahydropyrimido[1,2-a]indole Hydrochloride (Vb). This compound was obtained as in the preceding experiment by acylation of 4.9 g (0.03 mole) of 4-methyl-1-phenylpyrazolidine with 4.4 g (0.03 mole) of cyclohexanecarboxylic acid chloride. Crude IVb (5.6 g) was refluxed for 36 h with 9.2 g (0.06 mole) of phosphorus oxychloride in 50 ml of absolute benzene, after which the resulting precipitate was removed by filtration and worked up as in the case of IIa to give 3.6 g (41% based on the starting pyrazolidine) of Vb with mp 254° (from absolute alcohol). UV spectrum: λ_{max} 214 and 268 nm (log ε 4.30 and 4.13). IR spectrum: 1890 cm^{-1} (C=N). PMR spectrum, δ, ppm: 1.1 (d, 3-CH_3), 1.77 (s, 10-pentamethylene), 2.24 (m, 3-CH), 2.80-4.10 (m, 2- and 4-CH_2), 6.60-7.70 (m, 4-H aromatic), and 8.20 (s, NH). Found %: C 70.6; H 7.7. $C_{17}H_{22}N_2 \cdot HCl$. Calculated %: C 70.9; H 7.7. The molecular weight of base VIb was 254 (by mass spectrometry). $C_{17}H_{22}N_2$. Molecular weight 254.

10-Hydroxy-3,10-dimethyl-2,3,4,10-tetrahydropyrimido[1,2-a]indole (VIII). A 6.1-g (0.04 mole) sample of phosphorus oxychloride was added to a solution of 4.65 g (0.02 mole) of 4-methyl-1-phenyl-2-isobutyrylpyrazolidine [1] in 50 ml of absolute benzene, after which the mixture was refluxed for 60 h. The resulting precipitate was removed by filtration and dissolved in water. The solution was made alkaline to pH ~9, and the product was extracted with ether. The precipitate that formed from the ether solution on standing was separated and recrystallized from benzene–heptane to give 1.55 g (36%) of VIII with mp 228-230°. No melting-point depression was observed for a mixture of this product with a genuine sample [1], and their IR and PMR spectra were completely identical.

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PORPHYRINS

III.* SYNTHESIS AND PROPERTIES OF PORPHYRINS WITH HYDROXYALKYL SUBSTITUENTS

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The corresponding porphyrin was synthesized from 1-bromo-2,7,13,17,19-pentamethyl-3,8-diethyl-12-[2-(methoxycarbonyl)ethyl]bila-a,c-diene. Cyclization of the biladiene in dimethyl sulfoxide is accompanied by bromination of the β position of the porphyrin. Treatment of some porphyrins containing an ester grouping with sodium borohydride leads to reduction of the latter. The reduction products in concentrated sulfuric acid form sulfates that exist in the stable "monocation" form.

Of the porphyrins that have appreciable pharmacological activity most study has been devoted to hematoporphyrin IX [2], which contains two α-hydroxyethyl substituents and two β-carboxyethyl substituents. In order to study the biological and physicochemical properties of porphyrins containing such substituents we synthesized a model porphyrin (I) from pyrroporphyrin methyl ester (II). Starting II was obtained by cyclization of bila-a,c-diene V, synthesized from dipyrrylmethenes III and IV, in o-dichlorobenzene or in dimethyl sulfoxide (DMSO)–pyridine by the method in [3, 4]. [See structure on top of next page.]

Whereas the cyclization of biladiene V in o-dichlorobenzene took place in conformity with the methods described in [3], the result of cyclization in DMSO–pyridine depended to a considerable degree on the method used to isolate the final product. Thus maintenance of V at room temperature for 3-4 days gave porphyrin II, which was isolated from the reaction mixture in 70-75% yield. A new porphyrin, a characteristic feature of which was the absence of fluorescence in UV light, was obtained when the cyclization was carried out above 80°C with access to air for several hours with subsequent vacuum evaporation of the reaction mixture. Analysis of the PMR and mass spectral data made it possible to unambiguously establish that the product was

*See [1] for communication II.

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