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INTRAMOLECULAR CYCLIZATION OF N-PHTHALYL- &-ARYL-&-ALANINE PHENYLHYDRAZIDE

UDC 547.752'756'759.3.4.07:542.94:543.422

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The reaction of N-phthalyl- $\beta$ -aryl- $\beta$ -alanine N'-methyl-N'-phenylhydrazides with phosphorus oxychloride (at  $\sim 80^{\circ}$ C) is accompanied by further transformations of the initially formed 2-aminoindole derivatives and leads to isoindolo[1',2':2,3]pyrimido[5,6-b]indole derivatives. Intermediate 2-aminoindoles were isolated at lower reaction temperatures. The hydrolysis of the isoindolo[1',2':2,3]pyrimido[5, 6-b]indole derivatives was studied. The structures of the compounds obtained were established on the basis of the PMR, IR, and UV spectra and the results of elementary analysis.

We have previously established [1] that the Kost reaction in the case of N-acyl- $\beta$ -phenyl  $\beta$ -alanine phenylhydrazides is accompanied by further transformations of the intermediately formed 2-aminoindoles, which lead primarily to 2-imino-3-benzylidene derivatives of indole.

Another example of an unusual transformation for phenylhydrazides of phthalimide derivatives of  $\beta$ -phenyl- $\beta$ -alanine (Ia,b) has been described in a brief communication [2]. It was found that the reaction of the indicated hydrazides with phosphorus oxychloride at 80-83°C does not lead to 2-aminoindole derivatives of the II type but rather exclusively to compounds with a cyclic structure - pyrimidoindoles IIIa,b. The structure of IIIa,b was confirmed by the results of physicochemical methods of investigation. Thus the IR spectrum of IIIa contains absorption bands at 1720 (C=O) and 1620  $\text{cm}^{-1}$  (C=N) but does not contain the absorption bands at 3220 (NH), 1770 and 1705 (phthalimide C=O group), and 1670 cm<sup>-1</sup> (hydrazide C=O) that are characteristic for starting hydrazide Ia. An unresolved multiplet of aromatic protons at 6.1-7.0 ppm is observed in the PMR spectrum of IIIa [in  $D_7$ -dimethylformamide ( $d_7$ -DMF)], and the spectrum contains a singlet with an intensity of one proton unit at 3.85 ppm and a singlet of three protons of a methyl group attached to a nitrogen atom at 2.05 ppm. The set of these data, as well as the results of elementary analysis and the data from the mass spectra, which contains a molecular-ion peak with m/z 363 (which corresponds to the value calculated for this compound), made it possible to assign the IIIa structure to the compound obtained. (Formula, top, following page.)

By varying the conditions for the rearrangement of hydrazide Ia, viz., by carrying out the reaction at lower temperature (~40°C), we isolated intermediate IIa, through a step involving the formation of which, as we assumed, the reaction proceeds; in addition to IIa, which was obtained in 70% yield, we also isolated IIIa in 6% yield. The structure of IIa was confirmed by spectral data. Broad absorption bands at 2500-3400 cm<sup>-1</sup>, which correspond to the absorption of the salt form of an amino group, and absorption bands at 1775, 1720,

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1685, and 1640 cm<sup>-1</sup>, which correspond to absorption bands of C=O, C=N, and C=C bonds, are present in its IR spectrum. The PMR spectrum of hydrochloride IIa recorded in CF<sub>3</sub>COOH contains a singlet on an N-CH<sub>3</sub> group at 2.87 ppm (3H), two doublets at 4.89 (1H) and 5.47 ppm (1H) due to coupling of the proton in the  $\beta$  position of indole and the methylidyne proton of the 3-( $\alpha$ -phenylphthalimido)methyl group, and an unresolved multiplet of aromatic protons at 6.58-7.83 ppm (13H). When hydrochloride IIa is heated in benzene or alcohol solution, it undergoes complete thermal cyclization to IIIa.

The hydrolysis of IIIa with an alcohol solution of hydrochloric acid gives 2-imino-3-benzylideneindoline IVa as the principal product; the IR spectrum of IVa is identical to the IR spectrum of an authentic sample [1], and all of the remaining physicochemical characteristics are in agreement. In addition, phthalic acid and diindolo[2,3-b;3',2'-e]pyridine VI were isolated in low yield from the reaction mixture after hydrolysis of IIIa. The formation of VI evidently occurs due to further transformation of benzylidene derivative IV, as in the case of reactions of 2-aminoindoles with benzaldehyde [3]. We assume that the hydrolysis of IIIa proceeds through an intermediate step involving the formation of 2-aminoindole IIa, which undergoes subsequent transformation to benzylidene derivative IVa. The mechanism of this transformation is evidently similar to the mechanism of the formation of 3-benzylideneindolines in the rearrangement of N-acyl- $\beta$ -phenyl- $\beta$ -alanine phenylhydrazides [1].



The rearrangement of N-phthalyl- $\beta$ -(p-methoxyphenyl)- $\beta$ -alanine N'-methyl-N'-phenylhydrazide (Ib) when it is refluxed in benzene leads to the formation of IIIb. The product at a lower temperature (36-40°C) is intermediate IIb, which is detected by means of thin-layer chromatography (TLC) but could not be isolated in sufficiently pure form for complete identification, since it is readily converted to IIIb during recrystallization. Benzylidene derivative IVb, the structure of which was confirmed by the set of physicochemical data, was isolated after crude hydrochloride IIb was refluxed in an aqueous alcohol solution.

Thus isoindolo[1',2':2,3]pyrimido[5,6-b]indole derivatives III are formed in the reaction of N-phthalyl- $\beta$ -phenyl- $\beta$ -alanine phenylhydrazides with phosphorus oxychloride as a result of further transformations of intermediate 2-aminoindoles II. The "anomalous" transformations described above are quite specific, since they occur only when an amino group (substituted) and an aryl group are simultaneously present in the  $\beta$  position of the acyl residue of hydrazides I. In the absence of an aryl group the reaction gives a 2-aminoindole derivative [4]. Similarly, no deviations from the normal course of the process occur when the amino group is one methylene link removed from the  $\beta$  position. Thus N-phthalyl- $\beta$ -phenyl- $\gamma$ -aminobutyric acid VII gives the corresponding 2-aminoindole VIII in good yield.



The structure of VIII was confirmed by the data from physicochemical method.

## EXPERIMENTAL

The UV spectra of solutions of the compounds in alcohol or chloroform were recorded with a Perkin-Elmer-402 spectrophotometer. The IR spectra of suspensions of the compounds in mineral oil were recorded with a Perkin-Elmer-577 spectrometer. The PMR spectra were recorded with a Tesla BS-467 spectrometer. The course of the reactions was monitored by chromatog-raphy on activity II  $Al_2O_3$  in a benzene-methanol system (10:1).

<u>N-Phthaly1- $\beta$ -pheny1- $\gamma$ -aminobutyric Acid N'-Methy1-N'-pheny1hydrazide (VII).</u> A 6.56-g (0.02 mole) sample of N-phthaly1- $\beta$ -pheny1- $\gamma$ -aminobutyry1 chloride was added with stirring and cooling to a mixture of 2.44 ml (0.0)2 mole) of N'-methy1-N'-pheny1hydrazine and 2.76 ml (0.02 mole) of triethy1amine in 30 ml of benzene, and the mixture was stirred for 2 h. The precipitate was removed by filtration, washed with water, and recrystallized from alcohol to give 4.7 g (57%) of a product with mp 178-180°C. IR spectrum: 3260 (NH); 1775, 1715 (phthal-imide C=0); 1670 cm<sup>-1</sup> (amide C=0). Found: C 72.2; H 5.7; N 9.6%. C<sub>25</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>. Calculated: C 72.6; H 5.6; N 10.1%.

Compounds Ia and Ib were similarly obtained.

<u>N-Phthalyl-B-phenyl-B-alanine N'-Methyl-N'-phenylhydrazide (Ia)</u>. This compound was obtained in 60% yield and had mp 162-164°C (from alcohol). IR spectrum: 3220 (NH); 1770, 1715; (phthalimide C=0): 1670 cm<sup>-1</sup> (amide C=0). Found: C 71.8; H 4.9; N 10.1%.  $C_{24}H_{21}N_{3}O_{3}$ . Calculated: C 72.2; H 5.3; N 10.5%.

<u>N-Phthalyl-ß-(p-methoxyphenyl)-ß-alanine N'-Methyl-N'-phenylhydrazide (Ib).</u> This compound was obtained in 58% yield and had mp 130-132°C. IR spectrum: 3340 (NH) 1770, 1710, 1665 cm<sup>-1</sup> (C=O). Found: C 69.6; H 6.0; N 9.3%.  $C_{25}H_{23}N_{3}O_{4}$ . Calculated: C 69.9; H 5.4; N 9.8%.

 $\frac{2-\text{Amino-1-methy1-3-}(\alpha-\text{pheny1-B-phthalimidoethy1})\text{ indole Hydrochloride (VIII).} A mixture of 4.13 g (10 mmole) of phenylhydrazide VII and 1.76 ml (20 mmole) of phosphorus oxychloride in 110 ml of absolute benzene was refluxed for 15 h, after which it was evaporated, and the residue was recrystallized from ethanol to give 2.6 g (60%) of a product with mp 257-258°C. IR spectrum: 2550-3200 (NH<sub>3</sub>): 1770, 1710 (C=O) 1690 cm<sup>-1</sup> (C=N). UV spectrum, <math>\lambda_{max}$  (log  $\varepsilon$ ): 226 (4.51) and 273 nm (3.76). Found: C 69.2; H 5.3; N 9.9%. C<sub>25</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>•HC1. Calculated: C 69.5; H 5.3; N 9.7%.

<u>13-0xo-6-methyl-11-phenyl-11,12a-dihydro-13H-isoindolo[1',2':2,3]pyrimido[5,6-b]indole</u> (<u>111a</u>). A mixture of 2 g (5 mmole) of N-phthalyl-β-phenyl-β-alanine N'-methyl-N'-phenylhydrazide (Ia) and 0.92 ml (10 mmole) of phosphorus oxychloride in 100 ml of absolute benzene was refluxed for 30 h, after which the solvent and excess phosphorus oxychloride were evaporated, and the crystalline residue was washed with benzene and recrystallized from absolute alcoholmethylene chloride (3:1) to give 1.2 g (66%) of a product with mp 259°C. IR spectrum: 1720 (C=O) and 1620 cm<sup>-1</sup> (C=N). UV spectrum (in alcohol),  $\lambda_{max}$  (log  $\varepsilon$ ): 226 (4.66), 300 (3.94), and 373 nm (4.05). Found: C 79.0; H 4.9; N 11.7%. M 363 (mass-spectral). C<sub>24</sub>N<sub>27</sub>N<sub>3</sub>O. Calculated: C 79.3; H 4.7; N 11.6%. M 363.

 $\frac{13-0\text{xo-6-methyl-ll-(p-methoxyphenyl)-ll,l2a-dihydro-l3H-isoindolo[1',2':2,3]pyrimido[5,$ 6-b]indole (IIIb). This compound, with mp 237-238°C, was obtained in 57% yield under conditions similar to those in the preceding experiment. IR spectrum: 1720 and 1610 cm<sup>-1</sup>. UV $spectrum (in CHCl<sub>3</sub>), <math>\lambda_{\text{max}}$  (log  $\varepsilon$ ): 270 (3.53), 379 (3.63), and 455 nm (3.67). Found: C 75.9; H 5.0; N 10.3%. C<sub>25</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>. Calculated: C 76.3; H 4.8; N 10.7%.

 $\frac{2-\text{Amino-l-methyl-3-}(\alpha-\text{phenylphthalimidomethyl)indole Hydrochloride (IIa).} A mixture of 1.8 g (4.5 mmole) of N-phthalyl-\beta-phenyl-\beta-alanine N'-methyl-N'-phenylhydrazide (Ia) and 0.82 ml (9 mmole) of phosphorus oxychloride in 30 ml of absolute methylene chloride was refluxed for 25 h, after which it was evaporated. Absolute alcohol (10 ml) was added to the residue, and the mixture was filtered to give 0.095 g (6%) of pyrimidoindole IIIa with mp 258-$ 

259°C. Its IR spectrum was identical to the IR spectrum of the compound obtained in the preceding reaction. The alcoholic filtrate was evaporated to half its original volume and cooled, and the precipitate was removed by filtration and washed with absolute ether to give 1.35 g (70%) of a product with mp 216-220°C. IR spectrum: 2500-3400 ( $MH_3$ ); 1775, 1715 (C=0): 1685 cm<sup>-1</sup> (C=N). UV spectrum,  $\lambda_{max}$  (log  $\varepsilon$ ) 221 (4.56) and 260 nm (3.99). PMR spectrum: (CF<sub>3</sub>COOH): 2.87 (3H, s, N-CH<sub>3</sub>), 4.89 (1H, d,  $\beta$ -CH), 5.47 (1H, d, -CH-N<), and 6.58-7.83 ppm (13H, m, aromatic). Found: C 68.3; H 5.0; N 9.6%. C<sub>24</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>•HCl. Calculated: C 68.9; H 4.8; N 10.0%.

Hydrolysis of 13-Oxo-6-methyl-11-phenyl-11,12a-dihydro-13H-isoindolo[1',2':2,3]pyrimido[5, 6-b]indole (IIIa). A mixture of 0.5 g (1.4 mmole) of IIIa, 15 ml of ethanol, and 7.5 ml of concentrated HCl was refluxed for 10 h, after which it was evaporated. A 10-ml sample of ethanol-ether (1:1) was added to the residue, and the yellow crystals were removed by filtration, washed with ether, and dried to give 0.25 g (65%) of 2-imino-1-methyl-3-benzylideneindoline hydrochloride (IVa) with mp 240°C (from ethanol). IR spectrum: 2200-3350 (=NH2), 1680 (C=N), and 1640 cm<sup>-1</sup> (C=C). Found: C 70.4; H 5.9; N 10.1%. C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>•HC1. Calculated: C 70.9; H 5.6; N 10.4%. The combined filtrate was evaporated, 15 ml of water was added to the residue, and the mixture was heated to the boiling point. The aqueous solution was decanted and evaporated to give 0.035 g (13%) of phthalic acid with mp 229-230°C. The IR spectrum of the acid obtained was identical to the spectrum of a genuine sample. Benzene was added to the water-insoluble residue, and the solution was dried with Na2SO4 and transferred to a column filled with  $A1_2O_3$  and eluted with benzene-hexane (1:1) to give 0.025 g (5%) diindolo[2,3-b; 3',2'-e]pyridine (VI) with mp 290-292°C and molecular weight (M) 361 (by mass spectrometry). C25H19N3. Calculated: M 361. According to the data in [5], this compound had mp 292-294°C.

 $\frac{2-\text{Imino-1-methyl-3-}(p-\text{methoxybenzylidene})\text{indoline Hydrochloride (IVb)}. A mixture of 0.86 g (2 mmole) of N-phthalyl-<math>\beta$ -(p-methoxyphenyl- $\beta$ -alanine) N'-methyl-N'-phenylhydrazide and 0.37 ml (4 mmole) of phosphorus oxychloride in 20 ml of absolute methylene chloride was refluxed for 22 h, after which it was evaporated, and the residue was dissolved in absolute alcohol. Absolute ether was added to the solution until it became turbid, after which it was cooled, and the resulting crystals were removed by filtration and dissolved in aqueous alcohol. The solution was refluxed with activated charcoal, after which the charcoal was removed by filtration, and the filtrate was cooled to give 0.4 g (66%) of hydrochloride IVb with mp 236-240°C. IR spectrum: 2500-3300 (=NH<sub>2</sub>), 1685 (C=N), and 1640 cm<sup>-1</sup>. PMR spectrum (CF<sub>3</sub>COOH): 3.0 (3H, s, N-CH<sub>3</sub>), 3.33 (3H, s, OCH<sub>3</sub>), and 6.3-7.7 ppm (8H, m, aromatic). Found: C 67.3: H 5.4; N 9.2%. C<sub>27</sub>H<sub>16</sub>N<sub>2</sub>O+HC1. Calculated: C 67.8; H 5.7; N 9.3%.

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