SYNTHESIS OF 2-AMINO-3-(ω-AMINOALKYL)INDOLES

A. N. Kost,* V. G. Zabrodnyaya, Yu. N. Portnov,
and V. G. Voronin

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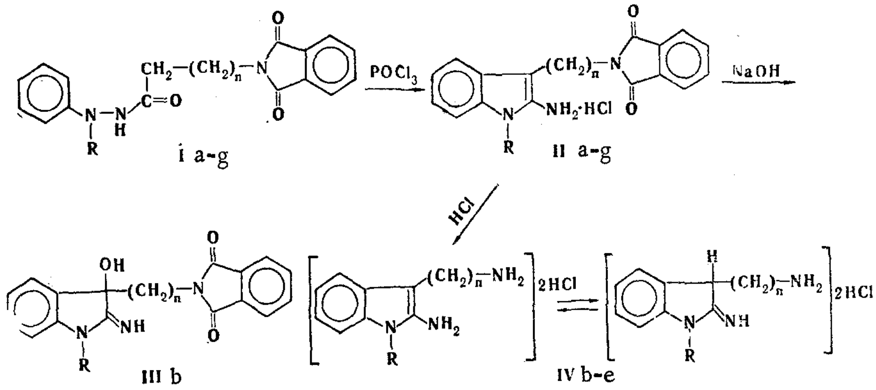
2-Amino-3-(ω-phthalimidoalkyl)indoles have been obtained by the rearrangement of ω-phthalimido acid β-phenylhydrazides under the action of $POCl_3$. The possibility has been studied of eliminating the phthalyl protective group from these compounds and a convenient method has been developed for obtaining 2-amino-3-(ω-aminoalkyl)indole dihydrochlorides. The behavior of the 2-amino-3-(ω-phthalimidoalkyl)indoles in alkylation reactions has been investigated.

We have shown previously that, on treatment with halides of phosphorus, 1-aryl-2-acylhydrazines with an α-methylene or methine group in the acyl residue rearrange into derivatives of 2-aminoindole [1, 2], although o,o'-disubstituted derivatives react in more complex fashion [3]. In this work we have investigated the possibility of using this new reaction for the synthesis of 2-amino-3-(ω-aminoalkyl)indoles. We have not succeeded in using in the reaction phenylhydrazides of ω-amino acids with amino groups unprotected or protected by acetyl or benzoyl groups, apparently because of side phosphorylation and cyclization reactions. The rearrangement takes place without complications in the case of phenylhydrazides of phthalimido acids (I). In this case, the corresponding 3-(ω-phthalimidoalkyl)indoles (II) are formed with yields of 60-80%.



I—IV a $R=CH_3$, $n=1$; b $R=CH_3$, $n=2$; c $R=CH_3$, $n=3$; d $R=CH_3$, $n=4$; e $R=CH_3$, $n=5$; f $R=C_6H_5$, $n=2$; g $R=CH_3$, $n=0$

The structure of compounds (II) is confirmed by their IR and UV spectra. Thus, the UV spectrum of the indole (IIe) in ethanol has absorption maxima at 219 and 263 nm (log ε 4.78, 3.82), which are characteristic for salts of 2-aminoindoles. Its IR spectrum shows a broad absorption band at 2600-3200 cm^{-1} corresponding to the vibrations of an ammonium group, and absorption in the 1715 and 1770 cm^{-1} regions which is assigned to the stretching vibrations of the carbonyl groups of a phthalimide ring. The mass spectrum of base (IIIe, $R = CH_3$, $n = 5$) obtained from the hydrochloride (IIe), contains the peak of the molecular ion with M^+ 377, which coincides with the value calculated for this compound. As is well known [4], 2-aminoindoles in the form of the free bases are readily oxidized by atmospheric oxygen with the formation of 3-hydroxy compounds. The length of the carbon chain of the acyl residue of a

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*Deceased.

M. V. Lomonosov Moscow State University. S. Ordzhonikidize Branch of the All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Kupavna. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 484-488, April, 1980. Original article submitted June 20, 1979.

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TABLE 1. N'Substituted N'-phenylhydrazides

Compound	mp, °C	IR spectrum, cm⁻¹	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
Ia	182—184	3250 1770 1720 1660	66,3	5,1	12,9	$C_{18}H_{17}N_3O_3$	66,9	5,3	13,0	65
Ib	142—144	3280 1770 1700 1660	67,8	5,8	12,4	$C_{19}H_{19}N_3O_3$	67,7	5,6	12,5	60
Ic	158—160	3290 1770 1710 1660	68,2	6,2	11,7	$C_{20}H_{21}N_3O_3$	68,4	6,0	11,9	84
If	198—200	3240 1770 1710 1670	71,5	5,2	—	$C_{24}H_{21}N_3O_3$	72,1	5,3	—	56
Id	124—127	3190 1775 1715 1660	68,6	6,2	11,7	$C_{21}H_{23}N_3O_3$	69,0	6,3	11,5	57
Ie	97—98	3190 1760 1710 1660	69,1	6,2	10,9	$C_{22}H_{25}N_3O_3$	69,6	6,6	11,1	62
Ig	195—196	3280 1780 1730 1680	65,8	4,9	13,1	$C_{17}H_{15}N_3O_3$	66,0	4,9	13,6	50

TABLE 2. Hydrochlorides of 2-Amino-3-(phthalimidoalkyl)indoles (II)

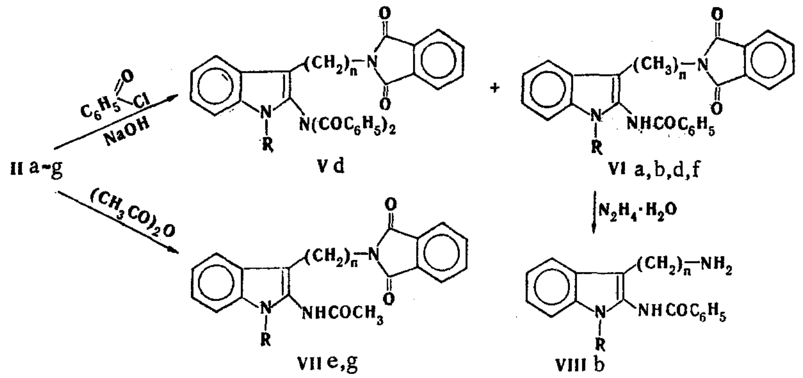
Compound	Reaction time, h (method of working up)	Reaction temperature, °C	mp, °C (from ethanol	UV spectrum		IR spectrum frequency, cm⁻¹	Found, %			Empirical formula	Calculated, %			Yield, %
				λ_{max}, nm	log ε		C	H	N		C	H	N	
IIa	18 (A)	80	225	220, 265	4,75, 3,89	3500—2600, 1786, 1710, 1618	63,5	5,3	12,6	$C_{18}H_{15}N_3O_2 \cdot HCl$	63,3	4,7	12,3	60
IIb	15 (A)	80	235 (decomp.)			3500—2600, 1785, 1716, 1615	64,7	5,7	11,2	$C_{20}H_{19}N_3O_2 \cdot HCl$	64,9	5,5	11,4	81
IIc	40 (B)	40	230 (decomp.)	218, 265	4,72, 3,85	3500—2600, 1770, 1725, 1615	63,7	5,1	12,2	$C_{19}H_{17}N_3O_2 \cdot HCl$	64,1	4,8	11,8	75
IId	18 (C)	80	212—214	219, 261	4,72, 3,87	3500—2600, 1770, 1710, 1610	65,2	5,9	11,4	$C_{21}H_{21}N_3O_2 \cdot HCl$	65,7	5,7	10,9	78
IIe	25 (C)	80	172—173	219, 263	4,78, 3,88	3570—2600, 1770, 1715, 1610	66,1	6,1	10,3	$C_{22}H_{23}N_3O_2 \cdot HCl$	66,4	6,0	10,6	70
IIf	42 (C)	40	159—163	220, 267	4,63, 3,96	3470—3050, 1770, 1710, 1630	68,7	5,1	10,4	$C_{24}H_{19}N_3O_2 \cdot HCl$	69,3	4,8	10,1	81
IIg	120 (C)	80	220 (decomp.)	224, 284	4,54, 3,92	3400—2600, 1780, 1730, 1615	62,1	4,6	13,1	$C_{17}H_{13}N_3O_2 \cdot HCl$	62,3	4,3	12,8	40

TABLE 3. Dihydrochlorides of 2-Amino-3-(ω-aminoalkyl)indoles (IV)

Compound	Reaction time, h	mp, °C (from ethanol)	UV spectrum		IR spectrum frequency, cm⁻¹	Found, %			Empirical formula	Calculated, %			Yield, %
			λ_{max}, nm	log ε		C	H	N		C	H	N	
IVb	16	225 (decomp.)	217, 270	4,33, 3,67	3500—2580, 1690, 1615	50,1	6,7	—	$C_{11}H_{15}N_3 \cdot 2HCl$	50,4	6,5		60
IVd	21	230 (decomp.)	214, 265	4,32, 4,06	3500—2600, 1685, 1610	53,6	7,5	14,1	$C_{13}H_{19}N_3 \cdot 2HCl$	53,8	7,7	14,4	48
IVc	21	220—224			3500—2600, 1680, 1610	51,5	7,1	14,7	$C_{12}H_{17}N_3 \cdot 2HCl$	52,2	6,9	15,2	55
IVe	23	237—240			3450—2600, 1680, 1615	54,5	7,9	13,5	$C_{14}H_{21}N_3 \cdot 2HCl$	55,1	7,6	13,8	60

hydrazide (I) has no fundamental influence on the occurrence of the reaction. However, while compounds (Ia-e) rearrange on boiling in benzene for 15-20 h, the complete conversion of the hydrazide (Ig) requires not less than 100 h. Here, apparently, a fundamental role is played by the steric effect of the phthalimide group.

In the Schotten-Baumann benzoylation of the 2-aminoindoles (II) in which n = 1, 2 the main products are the monobenzoyl derivatives (VI). A small amount of the dibenzoyl derivative as impurity is readily eliminated by recrystallization. In the case of compound (IId), however, a mixture of the dibenzoyl and monobenzoyl derivatives (Vd) and (VId) in a ratio of 2:1 is formed. A tendency to form diacyl derivatives is characteristic for 2-aminoindoles [5].



It was impossible to remove the protective phthalyl group from compound (II) by hydrazinolysis because of pronounced resinification of the reaction mixture. The best method of obtaining the dihydrochlorides of the aminoindoles (IV) proved to be the hydrolysis of compounds (II) in 20% hydrochloric acid followed by the elimination of the water by distillation. Under these conditions, no hydrolysis of amide fragment with the formation of oxindole, as might have been expected [6], was observed. The yields of compounds with (IV) amounted to 50-60%.

The UV spectrum of compound (IVa) contains absorption maxima at 217 and 270 nm (log ε 4.33, 3.67). The IR spectrum contains broad absorption bands at 2580-3500 cm^{-1}, corresponding to the vibrations of ammonium groups, and a strong absorption band at 1690 cm^{-1} corresponding to the C=N vibrations in the protonated imino form. The existence of compounds (IV) in the imino form is confirmed by the PMR spectra in which, in addition to all the other signals, there are two broadened signals of protons at a nitrogen atom (8.01-8.70 ppm), which indicates a considerable double bondedness of the α-carbon atom with the exocyclic nitrogen atom.

It proved possible to eliminate the phthalyl protective group by hydrazinolysis only in the case of the N-acylamino derivatives (VI). Under these conditions, no simultaneous splitting out of the acyl groups was observed. The structure of the compounds so obtained was confirmed by physicochemical methods. Thus, the IR spectrum of compound (VIIIb) has absorption bands at 3305 and 3380 cm^{-1} (NH) and 1660 cm^{-1} (C=O), while the absorption bands at 1705 and 1760 cm^{-1} present in the spectrum of the initial phthalimidoalkyl derivative (VIb) have disappeared. The mass spectrum of the base (VIIIb), showing the peak of the molecular ion corresponding to that calculated for this compound, confirms its structure.

Thus, the rearrangement of ω-amino acid β-phenylhydrazides can serve as a convenient method for synthesizing 3-aminoalkyl derivatives of 2-aminoindole.

EXPERIMENTAL

UV spectra were taken on a Perkin-Elmer 402 spectrophotometer in ethanol and IR spectra on a Perkin-Elmer 577 instrument in the form of mulls in paraffin oil. PMR spectra were recorded on a Tesla 467 instrument in CF_3COOH. Mass spectra were obtained on a MKh-1303 instrument with direct introduction of the sample into the ion source at an ionizing voltage of 30 eV. The course of the reactions was monitored by chromatography on Al_2O_3 [benzene–methanol (10:1)].

N'-Substituted N'-phenylhydrazides of ω-Amino Acids (Ia-g, Table 1). With cooling and stirring, 0.1 mole of an ω-phthalimido acid chloride was slowly added to a mixture of 0.1

mole of the appropriate N-substituted phenylhydrazine and 0.1 mole of triethylamine in 50 ml of absolute benzene. The mixture was stirred for 2 h, and the precipitate was filtered off, carefully washed with water, and recrystallized from ethanol.

Hydrochlorides of 2-Amino-3-phthalimidoalkylindoles (IIa-g, Table 2). A mixture of 0.01 mole of the appropriate phenylhydrazine (I) and 0.02 mole of phosphorus oxychloride in 50 ml of absolute benzene or methylene chloride was boiled. The end of the reaction was determined chromatographically from the disappearance of the spot of the initial phenylhydrazide. Then the reaction mixture was worked up by one of the following methods.

A. In the case of compounds (IIa) and (IIc), the precipitate was filtered off, washed with absolute benzene, and dissolved in ethanol with heating, and the solution was treated with activated carbon, boiled for 15 min, and the carbon filtered off. The hydrochlorides (IIa) and (IIc) were obtained from the filtrate after cooling.

B. In the case of (IIb), the solvent and the excess of phosphorus oxychloride were evaporated off, and the residue was treated with ether and was cooled to 0°C, and the resulting precipitate was filtered off.

C. The solvent and the excess of phosphorus oxychloride were evaporated off, the residue was treated with 30 ml of ethanol and inactivated carbon, the mixture was boiled for 15 min, the carbon was filtered off, the filtrate was cooled, and the precipitate of a hydrochloride (IId-g) was filtered off.

Dihydrochlorides of 2-Amino-1-methyl-3-(ω-aminoalkyl)indoles (IVb-e, Table 3). A mixture of 0.01 mole of the appropriate hydrochloride (II) and 60 ml of 20% hydrochloric acid was boiled and was then cooled, the phthalic acid was filtered off, the filtrate was evaporated to dryness, the residue was dried in vacuum over P_2O_5, 5 ml of absolute ethanol was added, and the precipitate that deposited was filtered off.

3-Hydroxy-2-imino-1-methyl-3-(phthalimidoethyl)indoline (IIIb). A solution of 0.36 g (1 mmole) of the hydrochloride (IIb) in 10 ml of water was made alkaline to pH~9 and was extracted with chloroform; the extract was allowed to stand for 6 h and was then dried with potassium carbonate, the chloroform was evaporated off, and the residue was recrystallized from ethanol, giving 0.13 g (40%) of compound (IIIb), mp 170-172°C. IR spectrum, cm^{-1}: 3340, 1775, 1715, 1650. Found: mol. wt. 335 (mass-spectrally). $C_{19}H_{17}N_3O_3$. Calculated: mol. wt. 335.

2-Acetylamino-1-methyl-3-(5-phthalimidopentyl)indole (VIIe). To 0.4 g (1 mmole) of the hydrochloride (IIe) in 5 ml of triethylamine was added 0.2 ml (2 mmole) of acetic anhydride, and the mixture was left at room temperature for 26 h. Then the triethylamine and excess of acetic anhydride were evaporated off, the residue was treated with 10 ml of water and was extracted with chloroform; the extract was washed successively with water, sodium bicarbonate solution, and water again, and it was dried with potassium carbonate and evaporated. Hexane was added to the residue, and the resulting precipitate was filtered off and recrystallized from ethanol. This gave 0.22 g (55%) of compound (VIIe), mp 162-164°C. IR spectrum, cm^{-1}: 3240 (NH), 1770, 1716, 1660 cm^{-1}. Found: C 70.6; H 6.4; N 10.4%. $C_{24}H_{25}N_3O_3$. Calculated: C 71.3; H 6.2; N 10.6%.

2-Acetylamino-1-methyl-3-phthalimidoindole (VIIg). A mixture of 0.1 g (0.3 mmole) of the hydrochloride (IIg) and 0.025 g (0.3 mmole) of sodium acetate in 3 ml of absolute benzene was treated with 0.03 ml (0.3 mmole) of acetic anhydride and the resulting mixture was left at room temperature for 70 h. After working up by the method described above and recrystallization from absolute ethanol, 0.05 g (50%) of compound (VIIg) was obtained. mp 236-237°C. IR spectrum, cm^{-1}: 3290, 1780, 1720, 1610. Found: mol. wt. 333 (mass-spectrally). $C_{19}H_{15}N_3O_3$. Calculated: mol. wt. 333.

2-Benzoylamino-1-phenyl-3-(2-phthalimidoethyl)indole (VIf). With stirring and cooling, 3.0 ml of benzoylchloride and 50 ml of a 2N solution of NaOH were added simultaneously to a solution of 2 g (5 mmole) of the hydrochloride (IIf) in 10 ml of water, stirring was continued for 1 h, the oily precipitate was separated off and treated with ether, and the resulting crystals were recrystallized from a mixture of ethanol and methylene chloride. This gave 1.94 g (80%) of compound (VIf), mp 250-251°C. IR spectrum, cm^{-1}: 3280, 1770, 1710, 1675 cm^{-1}. Found: C 76.8; H 4.6%. $C_{31}H_{23}N_3O_3$. Calculated: C 76.7; H 4.7%.

2-Benzoylamino-1-methyl-3-phthalimidomethylindole (VIa). This was obtained in a similar manner to the preceding compound by the benzoylation of 2.4 g (7 mmole) of the hydrochloride (IIa) with 5 ml of benzoyl chloride in the presence of 40 ml of a 2N solution of NaOH. This give 1.85 g (65%) of compound (VIa), mp 197-198°C (from a mixture of ethanol and methylene chloride). IR spectrum, cm^{-1}: 3340 (NH), 1760, 1705, 1680. Found: mol. wt. 409 (mass-spectrally). $C_{25}H_{19}N_3O_3$. Calculated: mol. wt. 409.

2-Benzoylamino-1-methyl-3-(2-phthalimidoethyl)indole (VIb). This was obtained in a similar manner to compound (VIf) from 3.7 g (0.011 mole) of the hydrochloride (IIb) and 6 ml of benzoyl chloride in the presence of 50 ml of a 2N solution of NaOH. This gave 2.9 g (70%) of compound (VIb), mp 203-205°C (from ethanol). IR spectrum, cm^{-1}: 3320, 1765, 1710, 1670. Found: mol. wt. 423 (mass-spectrally). $C_{26}H_{21}N_3O_3$. Calculated: mol. wt. 423.

Benzoylation of 2-Amino-1-methyl-3-(4-phthalimidobutyl)indole Hydrochloride. The benzoylation under conditions similar to those for (VIf) of 3 g (7.8 mmole) of the hydrochloride (IId) gave 2.5 g of a mixture of two substances, which were separated on a column of alumina (benzene–methanol (10:1) system). A substance with R_f 0.76 (1.8 g) was identified as 2-(dibenzoylamino)-1-methyl-3-(4-phthalimidobutyl)indole (Vd), mp 165-166°C (from ethanol). IR spectrum cm^{-1}: 1775, 1710, 1605 cm^{-1}. Found: C 74.9; H 4.9; N 7.7%. $C_{35}H_{29}N_3O_4$. Calculated: C 75.6; H 5.2; N 7.6%. A substance with R_f 0.52 (0.7 g) was identified as 2-(benzoylamino)-1-methyl-3-(4-phthalimidobutyl)indole (VId), mp 154-155°C (from a mixture of ethanol and methylene choloride). IR spectrum, cm^{-1}: 3270 (NH), 1770, 1710, 1610. Found: mol. wt. 451 (mass spectrally). $C_{28}H_{25}N_3O_3$. Calculated: mol. wt. 451.

3-(2-Aminoethyl)-2-benzoylamino-1-methylindole (VIIIb). To 1.8 g (4.0 mmole) of the (phthalimidoethyl)indole (VIb) in 100 ml of ethanol was added 2.5 ml of hydrazine hydrate, and the mixture was boiled for 2 h. Then the ethanol was evaporated off and the residue was treated with 30 ml of 1 N NaOH solution, and the material that had not dissolved was filtered off and recrystallized from ethanol to give 0.75 g (60%) of compound (VIIIb), mp 169-171°C. IR spectrum, cm^{-1}: 3305, 3380, 1660. Found: C 73.9; H 6.7%; mol. wt. 293 (mass-spectrally) $C_{18}H_{19}N_3O$. Calculated: C 73.8; H 6.5%; mol. wt. 293.

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