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SYNTHESIS OF THE ESTERS OF 1-ALKYL-2-AMINOINDOLYL-3-ACETIC ACIDS BY THE KOST REACTION

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The reaction of the esters of N-alkyl-N-phenylhydrazinocarbonylpropionic acids with phosphorus oxychloride in dioxane or with phosgene in benzene leads to the formation of the esters of 1-alkyl-2-aminoindolyl-3-acetic acids and of the corresponding N-alkyl-N-phenylaminosuccinimides.

The rearrangement of the arylhydrazides of ω-substituted carboxylic acids by the action of phosphorus halides is the main method for the synthesis of 2-aminoindol derivatives which have a functionally substituted alkyl radical in position 3 [1]. However, an attempt to synthesize 1-methyl-2-aminoindolyl-3-acetic acid by the reaction of the N-methyl-N-phenylhydrazide of ω-carbomethoxypropionic acid (1c) with an excess of phosphorus oxychloride gave only the product of intramolecular acylation: N-methyl-N-phenylaminosuccinimide (IIIa) [2].

We have shown earlier that solutions of phosgene in organic solvents or of phosphorus oxychloride in dioxane are mild and effective reagents for the Kost rearrangement [3]. However, the reaction of arylhydrazides of phenylacetic acid with phosgene leads to benzocarbolone derivatives, evidently due to acylation of the intermediate 2-aminoindole by an excess of the reagent, followed by cyclization [4].

It was therefore of interest to synthesize a series of derivatives of N-substituted phenylhydrazinocarbonylpropionic acids and to study their reaction with solutions of phosgene and phosphorus oxychloride at different temperatures with the aim of synthesizing the 1-alkyl-2-aminoindolyl-3-acetic acids which represent amino derivatives of heteroauxine and which are very interesting from a pharmacological standpoint.

The substituted phenylhydrazinocarbonylpropionic acids Ia,b were obtained by the reaction of arylhydrazines with succinic anhydride. They represent highmelting crystalline substances, insoluble in nonpolar organic solvents and water (Table 1). The acid esters Ic-e, having substituents at the nitrogen atom and the carboxyl group of different volume, were synthesized by the acylation of the arylhydrazines with the chloroanhydrides of the corresponding ω-alkoxycarbonylpropionic acids in the presence of triethylamine.

The structure of the synthesized *N*-substituted phenylhydrazinopropionic acids Ia,b and their esters Id,e was confirmed by IR spectroscopy. The mass spectra of compounds Ia,b,d,e, bombarded with rapid atoms (BRA), show intensive peaks with *m/z* M + H (Table 1). The PMR spectra of compounds Ia-e show two signals each of the protons of the amide fragments HNCO. In the case of the methyl derivatives Ia,c two singlet signals each of the N-methyl protons are also recorded. This is due to the existence of two forms of the molecules Ia-e in solution, caused by the hindered rotation around the C – N amide bond. The ratio of the surface areas of the HNCO signals corresponds to the ratio of the anti- and syn-isomers (Table 3). Sterically more favorable is the anti- configuration of the bulky N-phenylalkyl fragment and of the propionic acid fragment with respect to the C – N bond. In the instance of the compounds with an N-methyl group Ia,c the ratio of the anti- and syn- isomers is 80:20. The replacement of the methyl group by bulkier benzyl groups in compounds Ib,d,e leads to the increase of this ratio to 90:10. An increase in the temperature of the solutions leads to the broadening and convergence of the HNCO signals in the spectra of compounds Ia-e and CH_3 for compounds Ia,c. The coalescence of the signals of N-methyl protons in the spectra of compound Ia is observed at 353 K.

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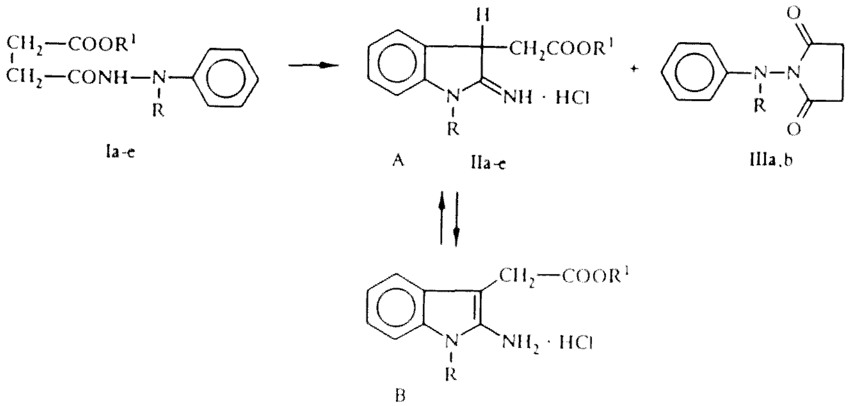

I, II a $R - CH_3$, $R^1 - H$; b $R - CH_2C_6H_5$, $R^1 - H$; c $R - R^1 - CH_3$; d $R - CH_2C_6H_5$, $R^1 - CH_3$,
e $R - CH_2C_6H_5$, $R^1 - i\text{-}C_3H_7$; III a $R - CH_3$; b $R - CH_2C_6H_5$

In the reactions of the hydrazino acids Ia,b with solutions of phosphorus oxychloride in dioxane at different temperatures the sole products were only the corresponding imides IIIa,b; on the other hand, the compounds Ia,b do practically not react with solutions of phosgene in benzene at temperatures up to 40°C during several days. At higher temperatures phosgene is rapidly volatilized from a solution in benzene. Evidently, the hydrazinocarbonylpropionic acids Ia,b react rapidly with phosphorus oxychloride to form the corresponding acylchlorophosphates and further, after intramolecular acylation of the amide nitrogen atom, the succinimides IIIa,b.

These data indicate also that N-alkyl-N-phenyl-aminosuccinimides IIIa,b do not undergo further heterocyclization, in distinction from their close structural analogs: the N-arylaminopyrrolidones-2, to form, at the conditions of Kost's reaction, derivatives of 2-oxotriptamines [5].

In the reactions of the methyl esters of hydrazinocarbonylpropionic acids Ic,d with solutions of phosphorus oxychloride in dioxane at the boiling point the imides IIIa,b are preferably formed. Only after prolonged standing at room temperature the hydrochlorides of the esters of 2-aminoindolyl-3-acetic acids IIc,d were separated with negligible yields (Tables 1 and 2). Higher yields of the esters of indolylacetic acids were obtained by heterocyclization in the presence of phosgene (1.3-1.5 mole/liter) in benzene. At these conditions the aminoindoles IIc,d and the imides IIIa,b were formed at approximately equal yields (Tables 1 and 2).

When the volume of the alkoxy group in the hydrazinoester (compound Ie) is increased, the rate of the side process of imide formation decreases and the yield of the corresponding ester of indolylacetic acid IIe increases to 63%.

Attempts to obtain aminoindolylacetic acids by alkaline hydrolysis of the corresponding esters were unsuccessful. A complex mixture of substances was formed at these conditions, probably due to rapid oxidation of the bases of 2-aminoindolyl-3-acetic acids by air oxygen. 1-Alkyl-2-aminoindolyl-3-acetic acids IIa,b were obtained with satisfactory yields by heating of their esters in concentrated hydrochloric acid (Table 1).

The hydrochlorides of indolyl-3-acetic acids IIa,b represent highmelting crystalline substances, poorly soluble in water and aqueous solutions of acids. The IR spectra of these compounds contain absorption bands of the salt-like amino group in the region 3400-2500 cm^{-1}, as well as absorption maxima of the carbonyl groups at 1730-1680 cm^{-1}. The mass spectra of BRA compounds IIa-e contain strong peaks with $m/z = M + H - HCl$. The PMR spectra (Table 3) show signals, broadened due to rapid change in the spectroscopic time scale, of methyne and methylene protons 3-H and 3-CH_2, belonging to the A and B tautomers which are present in commensurate quantities. The PMR spectra in the presence of trifluoroacetic acid are characterized by two multiplets of signals. The methyne protons 3-H are shown as triplets, the methylene 3-CH_2 as doublets with vicinal KSSV 4.4. Hz.

EXPERIMENTAL

The IR spectra of suspensions of the obtained substances in Vaseline oil were recorded on a Specord IR-75 spectrometer. The mass spectra of the substances, bombarded with rapid argon atoms (energy 5 kV), in glycerol matrices were

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	T mp °C	IR spectrum, cm^{-1}	Mass spectrum, m/z	Yield, %
Ia	$C_{11}H_{14}N_2O_3$	145...148	3180, 1700, 1640, 1600	223 (M + H)	91
Ib	$C_{17}H_{18}N_2O_3$	185...187	3190, 1700, 1640, 1600	299 (M + H)	82
Id	$C_{18}H_{20}N_2O_3$	75...77	3260, 3200, 1730, 1670, 1600	313 (M + H)	59
Ie	$C_{20}H_{24}N_2O_3$	79...80	3190, 1710, 1670	34 (M^+)	46
IIa	$C_{11}H_{12}N_2O_2 \cdot HCl$	220...222	3400...2500, 1730, 1720, 1680, 1610	205 (M + H - HCl)	94
IIb	$C_{17}H_{16}N_2O_2 \cdot HCl$	190...193	3300...2500, 1700, 1680, 1600	281 (M + H - HCl)	94
IIc	$C_{12}H_{14}N_2O_2 \cdot HCl$	214...216	3200...2700, 1720, 1690, 1610	219 (M + H - HCl)	47
IId	$C_{18}H_{18}N_2O_2 \cdot HCl$	197...200	3200...2700, 1730, 1690, 1600	295 (M + H - HCl)	52
IIe	$C_{20}H_{22}N_2O_3 \cdot HCl$	208...209	3200...2500, 1720, 1680	322 (M - HCl)	63
IIIb	$C_{17}H_{16}N_2O_2$	128...130	1705, 1590	280 (M^+)	74

TABLE 2. Heterocyclization of Esters of N-Alkyl-N-phenylhydrazinocarbonylpropionic Acids

Compound	Reagent/solvent	T, °C	Yield, %	
			Aminoindole II	Imide III
Ic	$POCl_3$/ dioxane	100	—	70
	″	20...22	22	76
	$COCl_2$/ benzene	20...22	47	48
	″	40...43	39	57
Id	$POCl_3$/ dioxane	20...22	22	74
	$COCl_2$/ benzene	20...22	49	48
	″	42...43	52	38
	$COCl_2$/ chloroform	20...22	37	34
Ie	$POCl_3$/ dioxane	60...62	63	28

recorded on a MI-1201E spectrometer. The electron-impact mass spectra were recorded on a MKh-1303 spectrometer by the direct introduction of the sample into the ionization chamber of the vaporizer; the energy of the ionizing electrons was 70 eV. The PMR spectra were recorded for 2% solutions of the substances in DMSO-D_6 or in a mixture of DMSO-D_6 with trifluoroacetic acid on a Tesla BS-587A with a working frequency of 80 MHz at 30°C, with tetramethylsilane as the internal standard. The progress of the reaction was checked and the purity of the obtained compounds was determined by TLC on Silufol UV-254 foils in the system chloroform–propanol-2 10:1.

N-Alkyl-phenylhydrazinocarbonylpropionic Acids (Ia,b). A mixture of 0.1 mole of succinic anhydride was refluxed in 50 ml absolute dioxane for 3-4 h until the disappearance of hydrazine from the reaction mass. When the reaction is finished the precipitate formed is filtered off, washed with hexane and dried in air (Table 1).

Esters of N-Alkyl-N-phenylhydrazinocarbonylpropionic Acids (Id,e). A solution of 0.1 mole N-benzyl-N-phenylhydrazine and 0.1 mole triethylamine in 200 ml dry toluene is treated dropwise with stirring and cooling with ice with a mixture of 0.1 mole of the chloride of the corresponding ω-alkoxycarbonylpropionic acid and 10 ml toluene; after this the reaction mixture is stirred for 2 h at 10-12°C and allowed to stand overnight at room temperature. The reaction mass is washed with water (2 × 100 ml), filtered, and evaporated in vacuum. The residue is triturated in hexane, filtered off, and recrystallized from a mixture of benzene and hexane (Table 1).

Reaction of N-Alkyl-N-phenylhydrazinocarbonylpropionic Acids and Their Esters (Ia-e) with Lewis Acids. A mixture of 0.01 mole of compounds Ia-e and 0.03 mole of phosphorus oxychloride in dioxane or of phosgene in benzene (substance-to-solvent ratio 1:10) is stirred until the disappearance of the initial substance from the reaction mass, followed by

TABLE 3. Parameters of PMR Spectra of Synthesized Compounds, b, ppm (J, Hz)

Compound	NHCO, br.s	H_{arom}, m	NR s	OR	CH_2CH_2 m	3-CH_2 d	3-H t
Ia *anti*,	9,85	6,6...7,3	3,06	12,0 (br.)	2,2...2,6		
syn	9,09		3,09				
79 : 21							
Ib *anti*,	9,95	6,6...7,7	4,62	12,0 (br.)	2,2...2,6		
syn	9,22						
90 : 10							
Ic *anti*,	9,89	6,6...7,3	3,06	3,60	2,2...2,6		
syn	9,13		3,09				
80 : 20							
Id *anti*,	9,93	6,6...7,7	4,63	3,59	2,2...2,6		
syn	9,19						
90 : 10							
Ie *anti*,	9,98	6,6...7,7	4,63	4,89, sept 1,17, d (6,3)	2,2...2,6		
syn	9,20						
88 : 12							
IIIb	—	6,6...7,7	4,77	—	2,2...2,6		
IIa*	—	6,9...7,6	3,50	—		3,35 (4,4)	4,45 (4,4)
IIb*	—	6,9...7,6	5,38	—		3,50 (4,4)	4,65 (4,4)
IIc*	—	6,9...7,6	3,50	3,50		3,44 (4,5)	4,51 (4,5)
IId*	—	6,9...7,6	5,35	3,47		3,54 (4,4)	4,70 (4,4)
IIc*	—	6,9...7,6	5,35	4,76, sept 0,99, d (6,2)		3,44 (4,0	4,74 (4,0)

*Spectrum in DMSO-D_6 with trifluoroacetic acid added.

TABLE 4. Elemental Analyses of Synthesized Compounds

Compound	Found, %				Calculated, %			
	C	H	N	Cl	C	H	N	Cl
Ia	59,2	6,5	12,4		59,4	6,3	12,6	
Ib	68,5	6,2	9,4		68,4	6,1	19,4	
Id	69,9	6,6	9,2		69,2	6,5	9,0	
Ie	71,0	6,8	8,2		70,6	7,0	8,2	
IIa	55,4	5,4	11,3	14,1	54,9	5,4	11,6	14,7
IIb	64,3	5,5	9,2	10,6	64,5	5,4	8,8	11,2
IIc	56,8	5,9	11,8	14,4	56,6	6,0	11,0	13,9
IId	65,6	5,8	8,3	11,0	65,4	5,8	8,5	10,7
IIe	66,2	5,8	8,1	9,2	66,9	6,5	7,8	9,9
IIIb	73,4	5,2	10,1		72,9	5,7	10,0	

evaporation in vacuum. When carrying out the reaction with phosphorus oxychloride, 20 ml dry toluene is added to the reaction mass and evaporated repeatedly to dryness in vacuum, removing traces of the reagent. The residue is triturated in dry ether, decanting it periodically. The crystalline precipitate of the aminoindole is filtered off, washed with dry ether, recrystallized from propanol-2, and dried in vacuum.

The ether extracts are combined and evaporated in vacuum. The residue is triturated in a small amount of hexane. The succinimide precipitate is filtered off and dried in air (Tables 1 and 2).

Hydrochlorides of 1-Alkyl-2-aminoindolyl-3-acetic Acids (IIa, b). A mixture of 0.01 mole of the corresponding ester and 20 ml of concentrated hydrochloric acid is refluxed with a reflux condenser for 2-4 h until the disappearance of the ester in the reaction mass; after this the mixture is cooled. The precipitate of the hydrochloride of the aminoindolyl-3-acetic acid is filtered off, washed with dry ether, and dried (Table 1).

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