SYNTHESIS AND PROPERTIES OF SOME TRYPTAMINE-CONTAINING CYCLOTRIPHOSPHAZENES

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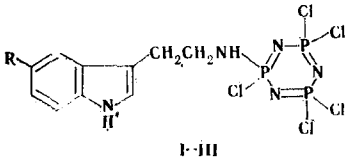
A number of cyclotriphosphazenes monosubstituted with tryptamine residues were synthesized. The conditions for the aminolysis of hexachlorocyclotriphosphazene with tryptamine, 5-nitrotryptamine, and 5-benzyloxytryptamine were examined. The physicochemical characteristics (the IR, UV, and NMR spectra) of the synthesized compounds are presented. It is shown by means of NMR spectroscopy that the substituted tryptamine-containing phosphazenes correspond to an AB_2 system (^{31}P); a difference in the chemical shifts in the ^{13}C spectra is observed for the C_α and C_β atoms of the tryptamine fragment.

We have previously undertaken the synthesis of derivatives of tryptamines, viz., 5-methoxytryptamine and α-methyltryptamine, that simultaneously contain phosphorus and nitrogen [1, 2]. It seemd of definite interest to establish whether the nature of the tryptamine affects the aminolysis of hexachlorocyclotriphosphazene and to obtain intermediates for the synthesis of new physiologically active compounds.

Hexachlorocyclotriphosphazene was subjected to aminolysis by tryptamine, 5-nitrotryptamine, and 5-benzyloxytryptamine:



I–III

I R=H; II R=NO_2; III R=$OCH_2C_6H_5$

We noted that a change in the reaction conditions, viz., the temperature, reaction time, and solvent, as compared with those that we previously used [1] does not have a substantial effect on the yields of final products. The most favorable conditions in the reaction of tryptamines with hexachlorocyclotriphosphazene were as follows: a reaction temperature of −10°C and a reaction time of 45 min with tetrahydrofuran (THF) or a mixture of chloroform with acetonitrile (7:1) as the solvent. Triethylamine was used as the hydrogen chloride acceptor in all of the reactions. The best results under identical conditions were achieved in the synthesis of the phosphazo derivative of 5-nitrotryptamine (II). The synthesis of the substituted 5-benzyloxytryptamine-containing phosphazene (III) proved to be more complex.

Chromatographic purification of the desired compounds with subsequent reprecipitation and recrystallization was necessary in all of the aminolysis reactions. The degree of purity of the starting hexachlorocyclotriphosphazene was of great importance for the aminolysis. Thus monosubstituted phosphazenes, which were crystallized with difficulty to give the products in low yields, were obtained in the reaction with the trimer purified by the method in [3]. The reaction of absolute pure (according to the ^{31}P NMR data and the results of x-ray diffraction analysis) hexachlorocyclotriphosphazene with 5-methoxy- and 5-nitrotryptamine led to crystalline tryptamine-containing phosphazenes in good yields.

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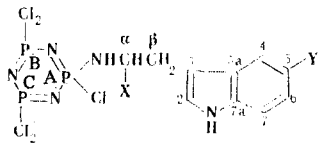
TABLE 1. ^{31}P and ^{13}C NMR Spectral Data for Monosubstituted Tryptamine-Containing Phosphazenes



Compound	Tryptamine fragment		^{31}P			^{13}C		
	X	Y	δ, ppm		$J_{P_A-P_B}$, Hz	δ, ppm		$J_{P_A-C_\alpha}$, Hz
			P_A	P_{B_2}		C_α	C_β	
I	H	H	−18,63	−21,43	48	39,17	24,32	8
II	H	NO_2	−17,97	−19,97	46	40,6	24,9	11,6
III	H	$OCH_2C_6H_5$	−18,71	−21,53	49	39,21	24,40	8
IV*	CH_3	H	−21,77	−19,27	46	31,60	46,47	—

*The chemical shift (δ) of the α-CH_3 group in the ^{13}C NMR spectrum is 19.98 ppm.

TABLE 2. Properties of the Monosubstituted Tryptamine-Containing Phosphazenes

Compound	R	mp, °C	R_f	Found, %					Empirical formula	Calc., %					Yield, %
				C	H	Cl	N	P		C	H	Cl	N	P	
I	H	102—103	0,97	25,9	2,6	38,0	14,4	19,9	$C_{10}H_{11}Cl_5N_5P_3$	25,4	2,3	37,6	14,8	19,7	30
II	NO_2	157—158	0,91	23,4	2,4	33,4	16,04	18,2	$C_{10}H_{10}Cl_5N_6O_2P_3$	23,2	1,9	34,3	16,2	18,0	40
III	$OCH_2C_6H_5$	114—115	0,97	36,2	2,8	29,5	11,6	16,4	$C_{17}H_{17}Cl_5N_5OP_3$	35,3	2,9	30,7	12,12	16,1	25

According to preliminary data from x-ray diffraction analysis, all of the monosubstituted tryptamine-containing cyclotriphosphazenes have a crystal structure with different interplanar distance that, at the same time, differs markedly from the structures of the starting phosphazene and tryptamines. A loss of crystallinity is observed on passing from the monosubstituted derivatives to the di- and polysubstituted derivatives, i.e., the tryptamine-containing phosphazenes with n > 1 are amorphous under the conditions that we used.

A comparison of the IR spectra of the monosubstituted phosphazenes showed the following. For the 5-benzyloxytryptamine- and tryptamine-containing phosphazenes the characteristic absorption band of the ring P=N–P bond appears at 1220 cm^{-1}, whereas it appears at 1215 cm^{-1} for the 5-nitrotryptamine-containing phosphazene; the vibrations of the P–N bond between the side chain of the tryptamine and the phosphorous atom of the phosphazene appear at 1190 cm^{-1} for the compound with R = NO_2, 1195 cm^{-1} for the compound with R = Bzl0, and 1200 cm^{-1} for the compound with R = H, i.e., in the case of the 5-nitro-tryptamine-containing phosphazene the characteristic absorption bands are shifted somewhat to the lower-frequency region. In the case of the monosubstituted derivative of α-methyltryptamine and cyclotriphosphazene (IV), on the other hand, one observes a shift to the near-IR region (1225 cm^{-1} for the vibrations of the ring P=N bond and 1200 cm^{-1} for the side chain P–N bond). The characteristic absorption bands of the vibrations of the remaining functional groups are also in complete agreement with the literature data [4]: The band at 1245 cm^{-1} belongs to the vibrations of the ether bond in the benzyloxy group of III, and the bands at 1530 and 1380 cm^{-1} belong to the vibrations of the NO_2 group of II. The stretching vibrations of the NH group of the indole ring appear at 3320-3350 cm^{-1}.

An examination of the UV spectra confirms the presence of tryptamine fragments in the reaction products; identical character is observed in the spectrograms of the starting tryptamines, and the tryptamine-containing cyclotriphosphazenes (absorption at 278-280 nm).

The ^{31}P NMR spectra of the monosubstituted tryptamine-containing hexachlorocyclotriphosphazene consist of multiplets, the general form of which corresponds to a three-spin system of the AB_2 type [2].

The chemical shifts and J_{P-P} spin–spin coupling constants were determined from a comparison of the experimental spectra and the spectra calculated by means of the Brucker NMRCAL standard program for simulation of the spectra. In all cases we observed agreement between the theoretical and experimental spectra – the difference in the frequencies of the individual signals did not exceed 1 Hz, which constitutes evidence for the correctness of the selected spin system.

A comparison of the ^{13}C NMR spectra for the various tryptamine-containing derivatives of hexachlorocyclotriphosphazene with the spectra of the starting tryptamines showed that a substantial difference in the chemical shifts is observed primarily for the α- and β-carbon atoms of the substituent. In addition, spin-spin coupling of the $^{31}P_A$ and C_α nuclei of the substituent is also a confirmation of the existence of a covaltent bond between the ring phosphorus atom of phosphazene and the indole derivative. The $J_{P_A-C_\alpha}$ spin-spin coupling constants are quite apparent in the ^{13}C spectrograms of the monosubstituted derivatives except for the derivative (IV) of α-methyltryptamine, for which the $J_{P_A-C_\alpha}$ SSCC may be smaller because of the inductive effect of the α-methyl group and therefore less appreciable. It is difficult to detect the J_{P-C} SSCC in the ^{31}P spectra because of the multiplicity of the signals and the great width of the resonance lines. The chemical shifts and SSCC for I-III, as well as for the derivative of α-methyltryptamine, are presented in Table 1.

EXPERIMENTAL

The constants of the synthesized compounds are presented in Table 2. The melting points were not corrected. The purity of the compounds described was verified by chromatography on Silufol UV-254 plates in chloroform–acetone (4:1) (A) and chloroform–acetone–petroleum ether (4:1:2.5) (B) systems; the chromatograms were developed with iodine and Erlich's reagent. The IR spectra of mineral oil suspensions and chloroform solutions of the compounds were recorded with a UR-20 spectrometer; the spectrometer was calibrated with respect to the spectrum of polystyrene. The UV spectra of $1 \cdot 10^{-4}$ mole/liter solutions of the compounds in ethanol were recorded with a Specord UV–vis spectrophotometer. The ^{13}C and ^{31}P NMR spectra were recorded at 40°C with a Brucker HX-90E spectrometer under pulse conditions with broad-band suppression of the spin–spin coupling with the protons; $CDCl_3$ was the solvent for I and III, while d_6-acetone was the solvent for II. The chemical shifts of the ^{13}C nuclei were reckoned from hexamethyldisiloxane as the internal standard, while the chemical shifts of the ^{31}P nuclei were reckoned relative to 85% phosphoric acid as the external standard. X-ray diffraction analysis was carried out with a DRON-3 diffractometer in Cu K_α emission with a βNi filter. All the reactions were carried out in freshly distilled anhydrous solvents. The latter were distilled in vacuo at 30-40°C. The triethylamine was purified beforehand to remove primary and secondary amines.

β-(3-Indolyl)ethylaminopentachlorocyclotriphosphazene (I). A 0.01-mole sample of triethylamine was added with vigorous stirring in a stream of argon to 0.01 mole of hexachlorocyclotriphosphazene in tetrahydrofuran (THF), after which, the mixture was cooled to −10°C and treated with 0.1 mole of tryptamine in THF. After 45 min, the precipitate was removed by filtration, the solvent was removed from the filtrate by distillation, and chloroform was added to the residue. The reaction mixture was washed with water, the organic layer was dried with magnesium sulfate, and the solvent was removed by distillation. The residue was dissolved in chloroform, and the solution was applied to a column (diameter 35mm) packed with silica gel and eluted with system A or B. The fractions containing the substance were collected, the solvent was removed by distillation, and the residue was triturated with hexane and crystallized from hexane.

β-(5-Nitro-3-indolyl)ethylaminopentachlorocyclotriphosphazene (II) and β-(5-benzyloxy-3-indolyl)ethylaminopentachlorocyclotriphosphazene (III) were similarly obtained. Compound II was crystallized from ether or ethyl acetate, while III was crystallized from hexane.

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SYNTHESIS OF PYRROLOQUINOLONES

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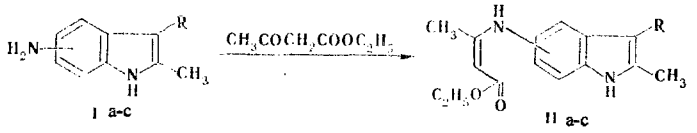
The condensation of 5- and 6-aminoindoles with diketene and acetoacetic ester was realized. A convenient method for the synthesis of pyrrolo[3,2-f]- and pyrrolo-[2,3-f]quinol-9-ones from 5- and 6-aminoindoles was developed. Under the influence of trifluoroacetic acid acetoacetic acid amides gave a mixture of 2,3,8-trimethylpyrrolo[2,3-g]quinol-6-one and 1,2,9-trimethyl-pyrrolo[3,2-f]quinol-7-one (in the case of 5-aminoindole) and a mixture of 2,3,5-trimethylpyrrolo[3,2-g]-quinol-7-one and 2,3,9-trimethylpyrrolo[2,3-f]quinol-7-one.

The interest in research on pyrroloquinolines, which has recently grown, is associated with their biological activity. For example, the pyrroloquinolines obtained from malonic ester have analgesic activity comparable to that of analgine [1]. The problem of the site of ring fusion arises in the formation of the pyrroloquinoline system on the basis of 5- and 6-aminoindoles, the molecules of which contain two free ortho positions relative to the amino group. Thus under acidic cyclization conditions the enamino ketones obtained from the amines and diketones indicated above give either linear or angular isomers [2]. The primary formation of one or the other pyrroloquinoline depends to a considerable extent on the steric requirements of the substituents in the 1 and 3 positions of the indole fragment. However, the thermal cyclization of the products of condensation of aminoindoles with ethoxymethylenemalonic ester proceeds regiospecifically to give pyrroloquinolines with only angular ring fusion, regardless of the nature of the substituent [1].

In a search for convenient methods for the synthesis of pyrroloquinolines that have a functional group in the pyridine ring we investigated the behavior of 5- and 6-aminoindoles in reactions with diketene and acetoacetic ester. The condensation of these amines with the latter may proceed at both the carbonyl group and at the carboxy group, and the formation of aminocrotonates or amides is consequently possible in this case. Crotonates II are readily obtained by refluxing aminoindoles with acetoacetic ester in the presence of traces of glacial acetic acid in absolute benzene. The structure of II was established on the basis of data from the PMR spectra (see Table 1).



I a-c II a-c

I–II a 5-NH_2, R = CH_3; b 5-NH_2, R = H; c 6-NH_2, R = CH_3

*Deceased.

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