SYNTHESIS OF PYRIMIDINE BETAINES WITH PHOSPHONIUM AND CYCLOAMMONIUM CATIONS

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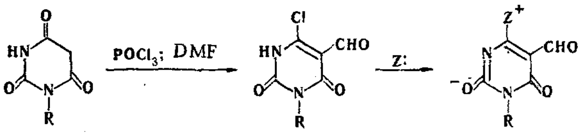
Previously undescribed pyrimidine betaines with cycloammonium and triphenylphosphonium cations were obtained. A study of the UV, IR, PMR, and mass spectra made it possible to draw a conclusion regarding the noncyclic structure of betaines stabilized by an intramolecular donor–acceptor interaction of the charge-transfer complex (CTC) type.

Continuing our study of the synthesis of organic systems containing an intramolecular ionic bond in order to ascertain the effect of structural changes in the anionoid and cationoid portions of the molecules of betaines on their physicochemical properties [1, 2] we synthesized pyrimidine betaines with triphenylphosphonium and cycloammonium cations (II and III). 6-Chloro-5-formyluracils (I) were obtained by chloroformylation of barbituric acids [3] and were subjected to reaction with the corresponding bases.



Ia-d   IIa-g, IIIa, b

I a R=C_6H_5; b R=p-C_6H_4—CH_3; c R=p-C_6H_4—OCH_3; d R=CH_3; II a Z=C_5H_5N; R=C_6H_5;
b Z=C_5H_5N; R=$C_6H_4OCH_3$; c Z=C_5H_5N; R=$C_6H_4CH_3$; d Z=C_5H_5N; R=CH_3;
e Z= β-carbamoylpyridine; Z=quinoline R=C_6H_5; g Z=isoquinoline; R=C_6H_5;
III a Z=$P(C_6H_5)_3$; R=C_6H_5; b Z=$P(C_6H_5)_3$; R=$C_6H_4OCH_3$

The reactions of I with nitrogen heterocycles (pyridine, quinoline, isoquinoline, etc.) proceed readily in dimethylformamide (DMF) when the mixtures are heated briefly. A singlet in the weak-field portion of the spectrum at δ 9.66 ppm, which corresponds to the signal of the proton of an aldehyde group, and signals of the α, γ, and β protons of a pyridinium cation at δ_1 9.20ppm, δ_2 8.76 ppm, and δ_3 8.20 ppm, respectively, are observed in the PMR spectrum of 1-phenyl-6-(1-pyridyl)-5-formyluracil-2-olate (IIa). The presence of a delocalized negative charge in betaines II is confirmed by the data from the IR spectra, in which a considerable shift to the high-frequency region (~50 cm^{-1}) of the vibrations of the carbonyl groups is observed in the case of their protonation or alkylation. This is characteristic not only for betaines with cycloammonium cations but also for triphenylphosphonium betaines (III). The latter were obtained via the scheme presented above by means of condensation with triphenylphosphine in acetonitrile.

In addition to the intense M^+ peak (18.0% of the maximum ion peak in the spectrum), which establishes the molecular ion, the mass spectrum of IIIa contains ion peaks with the following mass numbers (m/e), which were assigned to the following fragments of the investigated molecule: 77 $(Ph)^+$, 91 [azatropylium cation], 119 $(PhNCO)^+$, 185 $(PPh_2)^+$; 262 $(PPh_3)^+$; and 447 $(M-HCO)^+$. The maximum peak in the spectrum is the fragment

TABLE 1. 1-R-6-Chloro-5-formyluracils

Compound	R	mp, °C	Found, %				Empirical formula	Calculated, %				Yield, %
			C	H	Cl	N		C	H	Cl	N	
Ia	C_6H_5	232—233	52,5	3,0	14,4	11,1	$C_{11}H_7ClN_2O_3$	52,7	2,7	14,2	11,2	63
Ib	p-CH_3—C_6H_4	243—244	54,2	3,5	13,3	10,6	$C_{12}H_9ClN_2O_3$	54,4	3,4	13,4	10,6	58
Ic	p-CH_3O—C_6H_4	202—203	51,5	3,3	12,6	10,1	$C_{12}H_9ClN_2O_4$	51,3	3,2	12,7	9,9	70
Id	CH_3	217—218	39,2	2,9	18,2	15,0	$C_6H_5ClN_2O_3$	38,2	2,6	18,8	14,8	60

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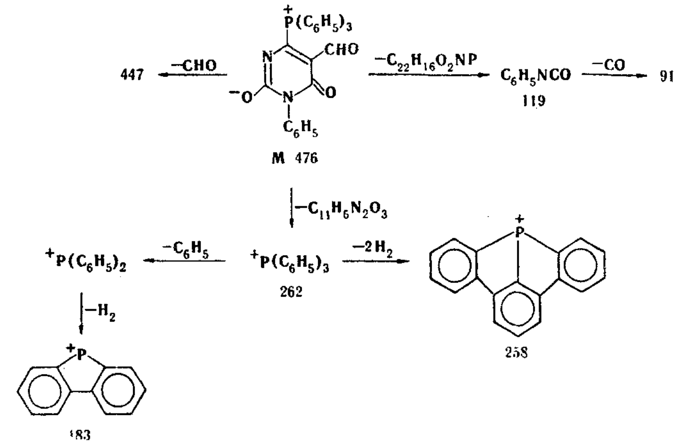
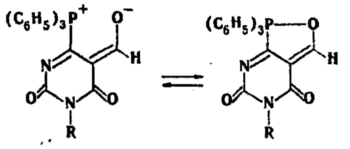
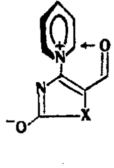
ion with m/e 183, which has a condensed structure. The most intense ion peaks are due to the subsequent fragmentation of the stabilized $(PPh_3)^+$ ion. This process is similar in many respects to the dissociative ionization processes that occur in the case of diphenylamines and tertiary amines with similar structures [4, 5]. The fragment ions with mass numbers 91, 119, $185[(M - HCO) - PPh_3]^+$, and 447 constitute evidence for the presence of a pyrimidine fragment [6]. Proceeding from the mass-spectrometric data, one can represent the fragmentation of the molecular ion of the triphenylphosphonium betaine (IIIa) by the following scheme:



In order to refine the structures of the triphenylphosphonium betaines (III), for which one cannot exclude the possibility of transformation to the cyclic form with a pentacovalent phosphorus atom in analogy with cyclic



A III B



IV

pentaarylphosphoranes [8] and dihydroxyphosphoranes [9, 10], we investigated their PMR spectra. Thus, in particular, a doublet with δ 9.40 ppm (J = 2.2 Hz), which was assigned to an aldehyde proton coupling with the phosphorus atom through four bonds, is observed in the PMR spectrum of IIIa. The observed complex pattern of the multiplet in the aromatic region of the spectrum from 7.30 to 7.66 ppm is due to the superimposition of the signals of the protons of the benzene ring bonded to the nitrogen atom and the signals of three benzene rings coupling with the phosphorus atom. The data obtained unambiguously indicate the absence in solution of a dynamic equilibrium of the $A \rightleftharpoons B$ type, for otherwise we would have observed the presence at weak field of two doublets with different constants of spin–spin coupling of the proton with the phosphorus nucleus through a system of three bonds in the cyclic form and a system of four bonds in the noncyclic form.

The electronic spectra of betaines IV (X = NPh, λ_{max} 450 nm) and IV (X = S, λ_{max} 400 nm), which, as we have previously established [7], display the properties of an intramolecular charge-transfer complex (CTC), differ substantially from those of the pyrimidine betaines (IIa, λ_{max} 328 nm) with respect to the position of the bands corresponding to the $n-\pi^*$ transitions. This is associated with branching of the chromophore in IIa, and a large degree of delocalization of the negative charge, which weaken the donor–acceptor interaction of the gegenions. The bands corresponding to the $n-\pi^*$ transition in IIa undergo a significant bathochromic shift (Δ39 nm) on passing from methanol to methylene chloride and vanish upon acidification. The observance of the Lambert–Beer law and the manifestation of negative solvatochromism constitute evidence for the presence in II of an intramolecular donor–acceptor interaction of the CTC type. An absorption band at 358 nm, which, in contrast to IIa, is not sensitive to a change in the polarity of the medium but vanishes when excess perchloric acid is present, appears in the spectrum of betaine IIIa, which contains a phosphonium cation. One cannot exclude the possibility that the indicated band is associated with an $n \rightarrow d$ transition as a result of an intramolecular space interaction of the phosphonium cation with the oxygen atom of the formyl group, since it is not observed in the spectrum of the starting chloroformylfuracil (Ia).

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra of methanol solutions of the compounds were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of DMSO solutions (2.5 ppm) of the compounds were obtained with a Bruker HX-90 spectrometer with GMSO as the internal standard. The mass spectra were recorded with a Varian MAT-311 spectrometer at an ionizing-electron energy of 70 eV.

1-R-6-Chloro-5-formyluracils (Ia-d). A reaction mixture consisting of the Vilsmeier reagent and 1-R-barbituric acid in a molar ratio of 1.5 : 1 was heated successively at 60-70°C for 4 h, at 110°C for 3.5 h, and at 135°C for 25-30 min, after which it was decomposed with ice, and the resulting precipitate was crystallized from chlorobenzene. In the case of Id the precipitate was crystallized from acetic acid. The physicochemical data for Ia-d are presented in Table 1.

1-Phenyl-6-(1-pyridyl)-5-formyluracil-2-olate (IIa). A mixture of 5 g (0.02 mole) of Ia in 6 ml of DMF and 3 ml (0.04 mole) of pyridine was heated at 60-70°C for 20-30 min, and the resulting precipitate was crystallized from aqueous methanol (1 : 1) to give 4.5 g (90%) of a product with mp 239-241°C. IR spectrum: ν_{CO} 1700, 1640-1680 cm^{-1}. UV spectrum (in methanol), λ_{max} (log ε): 246 (4.34); 295 (4.04); 328 nm (3.97). Found: C 65.8; H 4.1; N 14.5%. $C_{16}H_{11}N_3O_3$. Calculated: C 65.6; H 3.8; N 14.3%.

Compounds IIb-d, which are presented below, were similarly obtained.

Perchlorate IIa. This compound had mp 285-286°C (from acetic acid). IR spectrum: ν_{CO} 1760, 1680-1720 cm^{-1}. UV spectrum (in methanol), λ_{max} (log ε): 251 (4.09); 292 (4.98); 330 nm (3.60). Found: Cl 8.8; N 11.3%. $C_{16}H_{11}N_3O_3 \cdot HClO_4$. Calculated: Cl 9.1; N 11.1%.

1-(p-Anisyl)-6-(1-pyridyl)-5-formyluracil-2-olate (IIb). This compound had mp 210-211°C (from ethanol). Found: C 63.0; H 4.2; N 13.2%. $C_{17}H_{13}N_3O_3$. Calculated: C 63.1; H 4.0; N 13.0%.

1-(p-Tolyl)-6-(1-pyridyl)-5-formyluracil-2-olate (IIc). This compound had mp 263-264°C (from ethanol). Found: C 66.5; H 4.7; N 13.9%. $C_{17}H_{13}N_3O_3$. Calculated: C 66.4; H 4.2; N 13.7%.

1-Methyl-6-(1-pyridyl)-5-formyluracil-2-olate (IId). This compound had mp 306-308°C (from DMF). Found: C 57.5; H 4.2; N 18.5%. $C_{11}H_9N_3O_3$. Calculated: C 57.1; H 4.9; N 18.2%.

1-Methyl-6-(β-carbamoyl-1-pyridyl)-5-formyluracil-2-olate (IIe). A mixture of 1.8 g (0.01 mole) of Id in 15 ml of DMF and 2.4 g (0.02 mole) of nicotinamide was refluxed for 30-40 min, and the resulting precipitate was crystallized from DMF to give 2 g (77%) of a product with mp 275-276°C. Found: C 52.2; H 4.0; N 20.3%. $C_{11}H_{10}N_4O_3$. Calculated C 52.5; H 3.6; N 20.1%.

1-Phenyl-6-(1-quinolyl)-5-formyluracil-2-olate (IIf). A mixture of 1.25 g (0.005 mole) of Ia in 10 ml of DMF and 1.18 ml (0.01 mole) of quinoline was heated at 60-70°C until all of the solid dissolved completely. The solution was then treated with ether (30-40 ml), and the resulting precipitate was crystallized from ethanol to give 1 g (58%) of a product with mp 220-223°C. Found: C 69.6; H 4.0; N 12.4%. $C_{20}H_{13}N_3O_3$. Calculated: C 69.9; H 3.7; N 12.2%.

1-Phenyl-6-(1-isoquinolyl)-5-formyluracil-2-olate (IIg). A mixture of 2.5 g (0.01 mole) of Ia, 2.56 g (0.02 mole) of isoquinoline, and 10-15 ml of DMF was heated at 70-80°C for 1.5 h, and the resulting precipitate was crystallized from methanol to give 1.2 g (35%) of a product with mp 265-267°C. Found: C 70.1; H 4.2; N 12.0%. $C_{20}H_{13}N_3O_3$. Calculated: C 69.9; H 3.7; N 12.2%.

1-Phenyl-6-triphenylphosphonia-5-formyluracil-2-olate (IIIa). A mixture of 1.3 g (0.005 mole) of triphenylphosphine, 1.25 g (0.005 mole) of Ia, and 20 ml of acetonitrile was refluxed for 20-30 min, after which it was cooled and treated with 30-40 ml of ether. The resulting precipitate was crystallized from methanol to give 1.6 g (68%) of a product with mp 308-310°C. IR spectrum: ν_{CO} 1695, 1625-1640 cm^{-1}. UV spectrum (in methanol), λ_{max} (log ε): 226 (4.60); 257 (4.28); 353 nm (4.02). Mass spectrum (m/e; the ion peaks with intensities that are 5% of the maximum peak in the spectrum are presented): 477 (5.7), 476 (18.0), 447 (5.5), 263 (1.42), 262 (58.7), 261 (14.7), 259 (22.1), 258 (30.4), 247 (13.7), 186 (9.0), 185 (29.7), 184 (20.4), 183 (100.0), 152.9 (11.9), 142 (20.4), 119 (24.3), 109 (7.2), 108 (70.5), 107 (19.7), 107 (19.7), 105 (9.6), 104 (5.5), 103 (5.3), 102 (6.6), 92 (5.0), 91 (10.9), 79 (16.1), 78 (17.1), 77 (30.4), 65 (5.2), 64 (6.4), 63 (5.7), 52 (10.56), 51 (17.4), 50 (8.9). Found: C 73.0; H 4.6; N 5.9; P 6.3%. $C_{29}H_{31}N_2O_3P$. Calculated: C 73.1; H 4.4; N 5.8; P 6.5%.

1-(p-Anisyl)-6-triphenylphosphonia-5-formyluracil-2-olate (IIIb). This compound, with mp 275-276°C (from ethanol), was obtained by the procedure used to synthesize IIIa. Found: C 70.8; H 4.8; N 5.7; P 6.3%. $C_{30}H_{23}N_3O_4P$. Calculated: C 71.1; H 4.5; N 5.5; P 6.1%.

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4-TRIFLUOROACETAMIDOBENZOTRIAZOLE N$_2$-2,3,4-TRI-O-ACETYL-β-D-RIBOPYRANOSIDE

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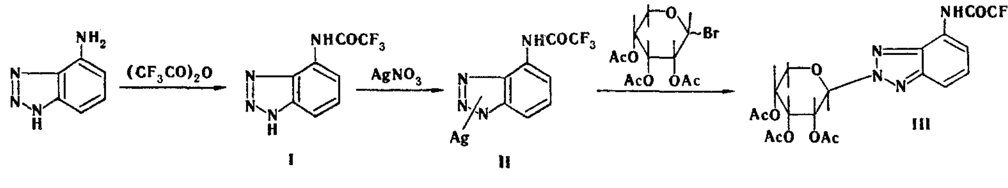
4-Trifluoroacetamidobenzotriazole (I) was synthesized by acylation of 4-aminobenzotriazole with trifluoroacetic anhydride under mild conditions in pyridine. The silver salt (II) of I was obtained by treatment of base I with an aqueous alcohol solution of $AgNO_3$. Condensation of silver salt II with 1-bromo-2,3,4-tri-O-acetyl-D-ribopyranoside leads to 4-trifluoroacetamidobenzotriazole N$_2$-2,3,4-tri-O-acetyl-β-D-ribopyranoside (III). The structure of nucleoside III was confirmed by its IR, UV, and PMR spectra.

Some benzotriazole derivatives – synthetic analogs of nucleosides – display antitumorigenic activity [1,2]. Up until now, 4-trifluoroacetamidobenzotriazole and nucleosides based on it were unknown.

4-Trifluoroacetamidobenzotriazole (I) was synthesized by acylation of 4-aminobenzotriazole with trifluoroacetic anhydride under mild conditions in pyridine. The silver salt (II) of base I was obtained by the action of an aqueous solution of silver nitrate on an alcohol solution of base I. Alkylation at the nitrogen atom of the 4-trifluoroacetamido group does not occur in the condensation of silver salt II with 1-bromo-2,3,4-tri-O-acetyl-D-ribopyranoside in toluene; this may evidently be due to the considerable deactivating effect of the strong electron-acceptor CF_3 group (σ_I 0.41 and σ_R 0.10) and p–π conjugation of the nitrogen atom with the oxygen atom of the adjacent carbonyl group. 4-Trifluoroacetamidobenzotriazole N$_2$-2,3,4-tri-O-acetyl-β-D-ribopyranoside (III) is therefore formed as a result of the reaction.



Completely protected nucleoside III gives one spot as a result of chromatography in various solvent systems and has an R_f value of 0.87 (Silufol UV-254). The IR spectrum displays the characteristic frequency of the vibration of the CF_3CONH group at 1715 cm^{-1} [3].

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