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SYNTHESIS OF PHOSPHORYLATED CARBAMOYLURACILS

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A series of previously unknown phosphorylated carbamoyluracils have been synthesized by the interaction of aliphatic and aromatic isocyanates of phosphorus(III) and phosphorus(V) acids with uracil. The structures of these compounds have been confirmed by IR and ^1H NMR spectroscopy.

The high antitumor activity of fluorouracil [1] and fluorafur [2] is the cause for the synthesis of many analogous substances [3]. Modification of 5-fluorouracil by introduction of various groups usually leads to a reduction of antitumor activity because the strong chemical bonds between the substituent and the heterocycle prevent biodistribution of the chemical within the organism. However some derivatives of 5-fluorouracil with weakly bonded substituents show no difference in antitumor activity when compared with 5-fluorouracil [4]. The N-alkylcarbamoyl-5-fluorouracils are included in this small group of compounds [4]. It was of interest in this connection to develop methods for the synthesis of the previously unknown phosphorylated carbamoyluracils to develop a database to establish structure–activity relationships.

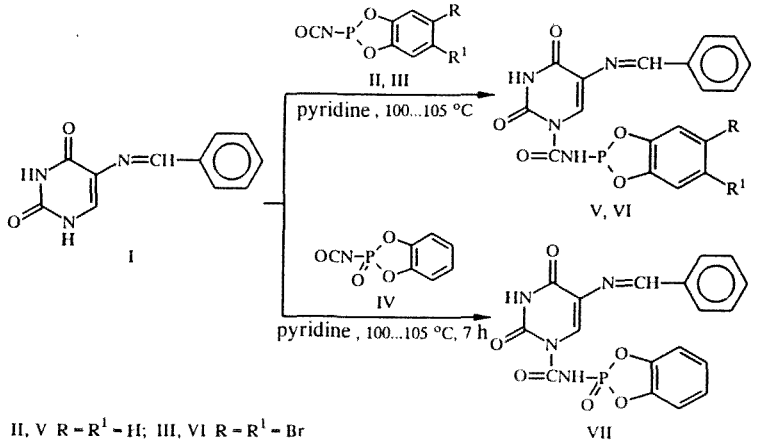
The basis of the synthesis is the reaction of uracil and its derivatives [5, 6] with an excess of the isocyanates of phosphorus(III) and phosphorus(V) acids [7]. Despite the presence of four nucleophilic centers in the uracil molecule (two nitrogen and two oxygen atoms) electrophilic substitution is usually quite selective: as a rule the hydrogen on the more nucleophilic $N_{(1)}$ atom is substituted first, then the one at the less nucleophilic $N_{(3)}$ atom, and finally the reaction occurs at the $C_{(5)}$ carbon atom [8-10].

The phosphorus atom is the reactive center when phosphorus(III) acid isocyanates react with nucleophiles. Scission, substitution of the isocyanate groups or addition at the phosphorus atom may occur.

Compounds containing an active hydrogen readily add to the isocyanate group in phosphorus(V) acid isocyanates. The thiocyanate group very rarely behaves as a pseudohalide in these compounds [7].

Since the uracil starting materials are practically insoluble at room temperature in all aprotic organic solvents, in contrast to the isocyanates of phosphorus acids, the synthesis of the phosphorylated carbamoyluracils was carried out in pyridine (V-VII) or dimethylformamide (XIII-XX) at 80-103°C. Compounds XXIII-XXVIII were synthesized by high temperature fusion of the reagents at atmospheric pressure.

In most cases addition of isocyanates II-IV occurred initially at atom $N_{(1)}$ of the uracil ring and then under more vigorous conditions at atom $N_{(3)}$.



II, V R = R¹ = H; III, VI R = R¹ = Br

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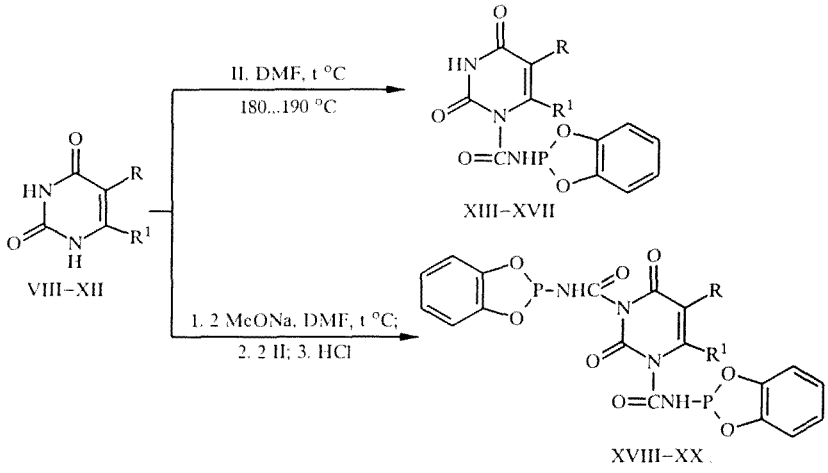
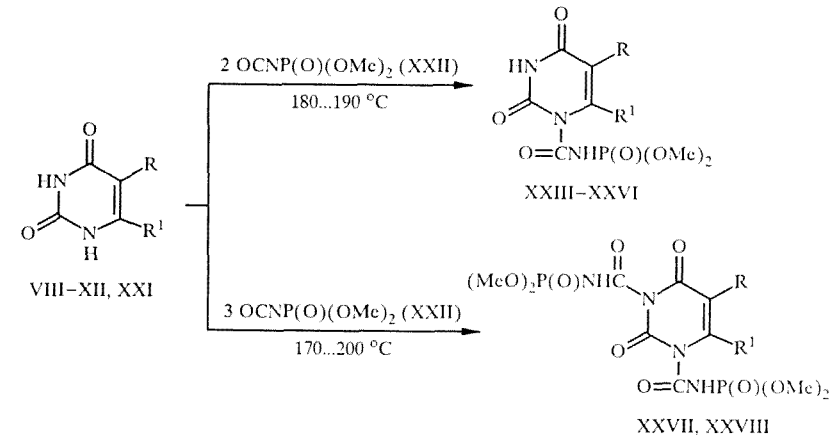
The sodium salts of the uracils VIII-X were used in the reaction with isocyanate II to obtain the 1,3-dicarbamoyl derivatives XVIII-XX in increased yield. The dianionic nature of the uracil ring in these salts explains their greater reactivity with the phosphorus acid isocyanates.



VIII, XIII, XVIII R = R^1 = H; IX, XIV, XIX R = Br, R^1 = H; X, XV, XX R = F, R^1 = H;
XI, XVI R = Me, R^1 = H; XII, XVII R = H, R^1 = Me

The carbamoyluracils V-VII and XIII-XX are cream colored hygroscopic, finely crystalline solids, insoluble in most aprotic organic solvents.

The 1-carbamoyl derivatives XXIII-XXVI and the 1,3-dicarbamoyl derivatives of uracil, XXVII and XXVIII, were produced by varying the reaction conditions and the mole ratio of the reagents when fusing together the uracils XXIII-XXVI and dimethyl isocyanatophosphonate XXII. The presence of an electron donating substituent in the uracil molecule facilitated the carbamoylation reaction considerably.



VIII, XXIII R = R^1 = H; IX, XXIV R = Br, R^1 = H; X, XXV R = F, R^1 = H; XI, XXVII R = Me, R^1 = H;
XII, XXVI R = H, R^1 = Me; XXI, XXVIII R = NO_2, R^1 = H

Compounds XXIII-XXV, XXVII and XXVIII are crystallizing oils while compound XXVI is crystalline. Yields are given in Table 1.

The compositions of compounds V-VII, XIII-XX, and XXIII-XXVIII were confirmed by elemental analysis and their structures by IR and ^1H NMR spectroscopy.

The IR spectra of compounds V-VII, XIII-XX and XXIII-XXVIII contained intense C=O absorptions (1680, 1715 and 1745 cm^{-1}) while P=O stretches (VII, XXIII-XXVIII) appeared as weak bands (1230-1250 cm^{-1}) while the $N_{(3)}$ stretches (V-VII, XIII-XVII, XXIII-XXVI) appeared in the 3200-3300 cm^{-1} region.

TABLE 1. Characteristics of Compounds V-VII, XIII-XX and XXIII-XXVIII

Compound	Molecular formula	M.p., °C	IR spectra (KBr)			^{1}H NMR spectra		Yield, %
			$\nu_{N(3)H}$	$\nu_{C=O}$	$\nu_{P=O}$	δ, ppm (J, Hz)	Solvent, standard*	
1	2	3	4	5	6	7	8	9
V	$C_{18}H_{13}N_4O_5P$	191...194	3200, 3500	1650, 1750	–	6,875...7,375 (9H, m, $2C_6H_5$), 7,687 (1H, s, $C_{(6)}$–H), 8,375 (1H, s, N=CH)	1	85
VI	$C_{18}H_{11}Br_2N_4O_5P$	210	3000, 3200	1710, 1745	–	6,9...7,29 (7H, m, $2C_6H_5$), 8,06 (1H, s, $C_{(6)}$–H), 8,65 (1H, s, N=CH), 10,24...11,25 (1H, s, $N_{(3)}$–H)	2	89
VII	$C_{18}H_{13}N_4O_6P$	97...101	3000, 3200	1710, 1745	1230, 1250	6,76...7,49 (9H, m, $2C_6H_5$), 7,89 (1H, s, $C_{(6)}$–H), 8,61 (1H, s, N=CH), 9,34 (1H, s, NHP), 11,18 (1H, s, $N_{(3)}$–H)	2	90
XIII	$C_{11}H_8N_3O_5P$	160...165	3000, 3200	1670 1710	–	5,7 (1H, s, NHP), 6,3...7,0 (4H, m, C_6H_5), 7,2 (1H, s, $C_{(6)}$–H)	3	25
XIV	$C_{11}H_7Br_2N_3O_5P$	160	3000, 3200	1670, 1680, 1710	–	6,7...7,3 (4H, m, C_6H_5), 8,1 (1H, d, $C_{(6)}$–H), 10,6 (1H, s, $N_{(3)}$–H)	1	35
XV	$C_{11}H_7FN_3O_5P$	118...120	3000, 3200	1670, 1680, 1710	–	5,68 (1H, s, NHP), 6,8...7,7 (4H, m, C_6H_5), 7,84 (1H, d, $C_{(6)}$–H, J = 8,0)	3	39
XVI	$C_{12}H_{10}N_3O_5P$	105...107	3000, 3200	1670, 1710	–	1,13...1,51 (3H, m, CH_3), 6,73...7,7 (4H, m, C_6H_5), 8,13 (1H, s, $C_{(6)}$–H)	1	23
XVII	$C_{12}H_{10}N_3O_5P$	90...93	3000, 3200	1670, 1680, 1710	–	2,00...2,6 (3H, m, CH_3), 5,7 (1H, s, $C_{(5)}$–H), 6,13...7,3 (4H, m, C_6H_5)	1	29

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
XVIII	$C_{18}H_{12}N_4O_8P_2$	160...163	–	1705, 1710	–	5,7 (1H, d, $C_{(5)}$–H, J = 8,0), 6,9...7,4 (10H, m, $2C_6H_5$), 7,7 (1H, d, $C_{(6)}$–H)	3	27
XIX	$C_{18}H_{11}BrN_4O_8P_2$	140...143	–	1705, 1710	–	6,8...7,5 (9H, m, $2C_6H_5$), 8,1 (1H, s, $C_{(6)}$–H)	3	49
XX	$C_{18}H_{11}FN_4O_8P_2$	145...148	–	1705, 1710	–	6,9...7,8 (8H, m, $2C_6H_5$), 8 (1H, d, $C_{(6)}$–H, J = 8,0)	3	55
XXIII	$C_7H_{10}N_3O_6P$	–	3000, 3200	1660, 1745	1230, 1280	3,46 (6H, d, $2OCH_3$), 5,6 (1H, d, $C_{(5)}$–H, J = 8,0), 7,2 (1H, d, $C_{(6)}$–H, J = 8,0)	1	25
XXIV	$C_7H_9BrN_3O_6P$	–	3000, 3200	1660, 1710, 1745	1230, 1280	3,68 (6H, d, $2OCH_3$, J = 19,2), 7,76 (1H, s, $C_{(6)}$– H)	1	26
XXV	$C_{10}H_{15}FN_4O_6P_2$	–	3000, 3200	1660, 1745	1230, 1280	3,745 (6H, d, $2OCH_3$, J = 13,6), 5,68 (1H, t, NHP), 7,55 (1H, d, $C_{(6)}$–H, J = 8,0)	1	14
XXVI	$C_8H_{12}N_3O_6P$	238...240	3000, 3200	1660, 1710, 1745	1130, 1280	6,12 (1H, s, $C_{(5)}$–H), 7,85 (3H, s, CH_3), 9,27 (1H, s, $N_{(3)}$–H)	2	25
XXVII	$C_{11}H_{18}N_4O_{10}P_2$	–	–	1660, 1745	1230, 1280	1,8 (3H, s, CH_3), 2,55 (3H, t, OCH_3, J = 8,0), 3,15 (3H, s, OCH_3), 3,62 (1H, m, NHP)	4	70
XXVIII	$C_{10}H_{15}N_5O_{12}P_2$	–	–	1660, 1745	1230, 1280	1,7 (3H, s, CH_3), 2,237 (3H, t, OCH_3, J = 6,7), 3,01 (3H, s, OCH_3), 3,62 (1H, m, NHP)	4	52,5

*1) CF_3COOH, HMDS; 2) DMSO-D_6; 3) D_2O; 4) pyridine, HMDS.

The ^1H NMR spectra of compounds XV, XX, and XXV contain a doublet at about 7.6-8.13 ppm ($^3J_{H,F}$ 8 Hz) corresponding to the hydrogen bonded to $C_{(6)}$ of the ring coupled to the fluorine atom. The spectra of compounds XXIII-XXVIII are characterized by triplets at 2.23-2.55 ppm ($J_{P,H}$ 6.7-8 Hz). Compounds V-VII, XIII-XVII and XXIII-XXVI have a broad singlet at 10.5-11.8 ppm corresponding to the $N_{(3)}$-H group. Assignments of all other signals are given in Table 1.

EXPERIMENTAL

^1H NMR spectra of compounds V-XXVIII were recorded with Tesla BS-486 (80 MHz) and BS-487C spectrometers in CF_3COOH, C_5H_5N, DMSO-D_6 and D_2O with hexamethyldisiloxane (HMDS) as internal standard. IR spectra were measured with Perkin-Elmer 325 and UR-20 spectrophotometers. TLC was carried with Silufol-254 strips. The uracil and isocyanate starting materials were synthesized by known methods [5-7]. Physicochemical and spectroscopic parameters and yields of compounds V-XXVIII are cited in Table 1.

Elemental analysis results for C, H, N, and P for the new compounds corresponded to the calculated values.

N-(4′,5′-Benzo-1′,3′,2′-dioxaphospolenocarbamoyl)-5-benzylideneiminouracil (V, $C_{18}H_{13}N_4O_5P$). Isocyanate II (0.015 mole) was added to a solution of iminouracil I (0.01 mole) in pyridine or N-methylpyrrolidone (40 ml). The mixture was heated to 100°C with stirring and kept for 7 h at this temperature. The mixture was cooled and kept at room temperature (10 h), the precipitate was filtered off, washed with small portions of acetonitrile and dried in vacuum.

Compounds VI ($C_{18}H_{11}Br_2N_4O_5P$) and VII ($C_{18}H_{13}N_4O_6P$) were prepared analogously from iminouracil (I) and isocyanates III and IV respectively.

N-(4′,5′-Benzo-1′,2′,3′-dioxaphospholenocarbamoyl)uracil (XIII, $C_{11}H_8N_3O_5P$). A mixture of uracil VIII (0.02 mole) and 2-isocyanato-4,5-benzo-1,3,2-dioxaphospholene (II) (0.03 mole) in dry DMF (50 ml) was heated to 100°C with stirring and kept at that temperature for 3 h. The solvent was removed in vacuum and the residual oil was dissolved in hot isopropanol (20 ml) and kept overnight in the cold. The precipitate was filtered off, washed with diethyl ether and dried in vacuum at 100°C.

Compounds XIV-XVII ($C_{11}H_7Br_2N_3O_5P$, $C_{11}H_7FN_3O_5P$, $C_{12}H_{10}N_3O_5P$, $C_{12}H_{10}N_3O_5P$) were prepared analogously from isocyanate II and uracils IX-XII respectively.

$N_{(1)}N_{(3)}$-Bis-(4′,5′-benzo-1′,3′,2′-dioxaphospholenocarbamoyl)uracil (XVIII, $C_{18}H_{12}N_4O_8P_2$). A. Sodium methoxide (0.04 mol) was added with stirring to a solution of uracil VIII (0.02 mole) in DMF (50 ml) at 100°C and the mixture was kept at this temperature for 0.5 h. The solvent was removed in vacuum and the solid residue was washed with isopropanol and dried in vacuum.

B. A mixture of the disodium salt of uracil VIII (0.02 mole) and dioxaphospholene II (0.06 mole) in dry DMF (50 ml) was stirred and heated to 100°C and then kept at that temperature for 3 h. The solvent was removed in vacuum. Methanol (100 ml) and conc. HCl (5 ml) were added to the solid residue and the mixture heated to boiling. The mixture was cooled, NaCl filtered off, and the solvent removed in vacuum. The residue was dissolved in hot ethanol (100 ml), filtered and kept in the cold overnight. The precipitate was filtered off, washed with ether and dried in vacuum at 60°C.

Compounds XIX ($C_{18}H_{11}BrN_4O_8P_2$) and XX ($C_{18}H_{11}FN_4O_8P_2$) were prepared analogously from isocyanate II and uracils IX and X respectively.

N-(Dimethoxyphosphorylcarbamoyl)uracil (XXIII, $C_7H_{10}N_3O_6P$). A mixture of uracil VIII (5 mmole) and isocyanate XXII (0.01 mole) was heated to 190°C and the molten mixture was kept at this temperature for 15-20 h. It was then cooled, washed with ether and the residue heated with ethanol. The solid which precipitated on cooling was filtered off.

Compounds XXIV ($C_7H_9BrN_3O_6P$), XXV ($C_{10}H_{15}FN_4O_{10}P_2$) and XXVI ($C_8H_{12}N_3O_6P$) were prepared analogously from isocyanate XXII and uracils IX, X and XII respectively.

$N_{(1)}$,$N_{(3)}$-Bis-(dimethoxyphosphorylcarbamoyl)-5-methyluracil (XXVII, $C_{11}H_{18}N_4O_{10}P_2$). A mixture of uracil XI (5 mmole) and the dimethyl ester XXII (15 mmole) was heated to 170-200°C and the molten mixture maintained at this temperature for 12 h. The mixture was cooled, dissolved in DMF and purified by boiling with activated charcoal. After removal of the solvent the oily residue was washed with ether and dried in vacuum to give a crystallizing oil.

Compound XXVIII ($C_{10}H_{15}N_5O_{12}P_2$) was made analogously from uracil XXI and isocyanate XXII.

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