SYNTHESIS AND PROPERTIES OF PYRIMIDINYLALKYLPHOSPHONIC ACIDS

COMMUNICATION 11. REACTION OF DIPHENYL URACIL PHOSPHATES WITH AMINES

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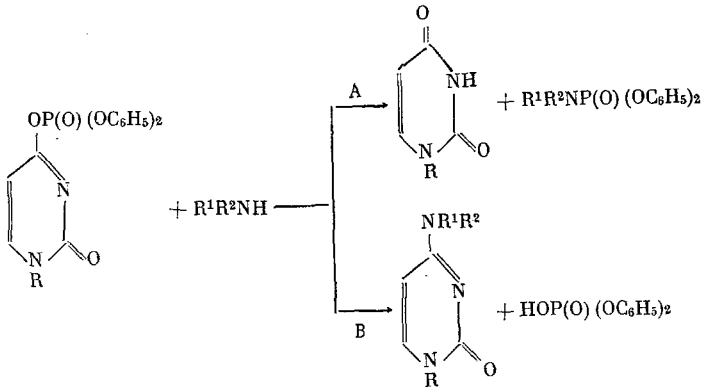
The reaction of diphenyl uracil phosphates [1] with amines is described in the present communication. It was established that the isomeric diphenyl 1-alkyluracil 4-phosphates, and the diphenyl 3-alkyluracil 2-phosphates and diphenyl 3-alkyluracil 4-phosphates, react with amines at 18-20°C, at times with heat evolution. The character of the formed products depends on the presence of a substituent on either the N^1 or N^3 atoms of the pyrimidine ring of the diphenyl uracil phosphates, and also on the position of the diphenylphosphonoxy group and the nature of the amine.

The diphenyl 1-alkyluracil 4-phosphates react with amines in two directions: with the formation of the 1-alkyluracil and the corresponding diphenyl amidophosphates (direction A), or with the formation of diphenylphosphoric acid and the corresponding 1-alkylcytosines (direction B).



In direction A the phosphorus atom is the reaction center, while in direction B it is the carbon atom of the pyrimidine ring. We determined the degree of conversion of diphenyl 1,6-dimethyluracil 4-phosphate (I) along directions A and B as a function of the basicity and structure of the amine taken for reaction. With Et_2NH (pK_a 10.93) 26% of ester (I) reacts along direction A, and 70% along direction B. With N-(o-tolyl)-piperazine (pK_a 9.8) 63% of ester (I) reacts along direction A, and 34.7% along direction B. Ammonia (pK_a 9.25) in either benzene or m-xylene medium fails to react at all along direction B, and gives diphenyl amidophosphate and 1,6-dimethyluracil in 95.5% yield (direction A). In contrast to ammonia, aniline (pK_a 4.58) reacts with (I) only along direction B, and here 1,6-dimethyl-N^7-phenylcytosine is formed in 93% yield. As a result, the presented data show that the direction of the reaction of amines with (I) is not determined unequivocally by the basicity of the amine.

The size of the substituent on the N^1 atom of the pyrimidine ring in the 1-alkyluracil 4-phosphate has little effect on the direction of the reaction of the latter with amines. Thus, diphenyl 1-[ω-(dibutylphosphono)butyl]uracil 4-phosphate (II) reacts with aniline the same as (I) only along direction B to give 1-[ω-(dibutylphosphono)butyl]-N^7-phenylcytosine in 69% yield.

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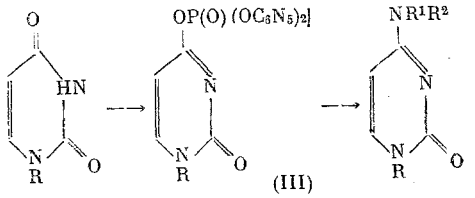
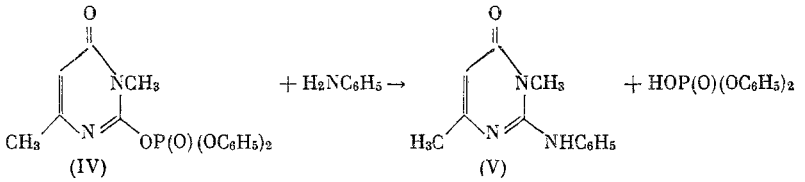
The reaction of the diphenyl 1-alkyluracil 4-phosphates with amines opens up a new route for going from the 1-alkyluracils to the 1-alkylcytosines. This route includes reacting the Na salts of the 1-alkyluracils with diphenyl chlorophosphate to give the diphenyl 1-alkyluracil 4-phosphates (III), and the subsequent amination of (III). The high, at times quantitative, yield of the (III) esters, and also the exceedingly mild conditions for the reaction of the latter with amines (0.5-1 h at 18-25°), make it possible to run the transformation of the 1-alkyluracils to the 1-alkylcytosines in one step without isolating the (III) esters.



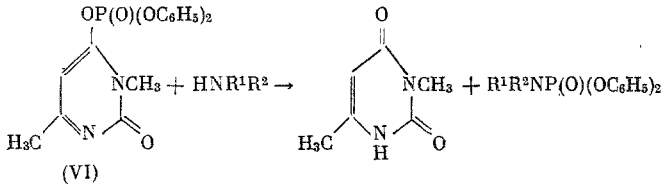
(III)

Diphenyl 3,6-dimethyluracil 2-phosphate (IV) reacts with aniline only at the C atom of the pyrimidine ring to give the corresponding isocytosine derivative (V).



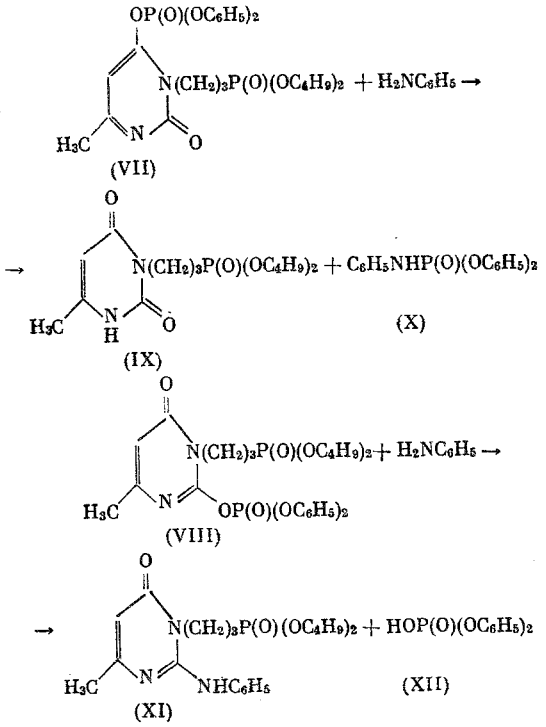
(IV) (V)

Diphenyl 3,6-dimethyluracil 4-phosphate (VI) reacts with aniline and with Et_2NH only at the phosphorus atom to give the corresponding diphenyl amidophosphates.



(VI)

A mixture of diphenyl 3-[ω-(dibutylphosphono)propyl]-6-methyluracil-4-phosphate (VII) and diphenyl 3-[ω-(dibutylphosphono)propyl]-6-methyluracil-2-phosphate (VIII) reacts with aniline to give a mixture of 3-[ω-(dibutylphosphono)propyl]-6-methyluracil (IX), diphenyl N-phenylamidophosphate (X), 2-phenylamino-3-[ω-(dibutylphosphono)propyl]-6-methyl-3,4-dihydro-4-pyrimidone (XI), and diphenylphosphoric acid



(VII) (IX) (X) (VIII) (XII) (XI)

(XII). The ratio of compounds (IX) and (XI) in the reaction mixture corresponds to the ratio of esters (VII) and (VIII) (established on the basis of the ^{31}P-NMR spectral data) in the starting mixture.

As a result, the isomeric diphenyl 3-alkyluracil 2-phosphates and diphenyl 3-alkyluracil 4-phosphates react with amines at a different electrophilic center. In addition, substantial differences exist in the character of the reaction of amines with the isomeric diphenyl uracil phosphates that have substituents on either the N^1 or N^3 atoms of the pyrimidine ring [for example, (I) and (VI)].

EXPERIMENTAL

All of the operations with the diphenyl uracil phosphates were carried out in a Dry Box in an argon atmosphere, dried over P_2O_5. The IR spectra were taken on a UR-10 spectrophotometer; the solids as Nujol mulls, and the liquids between KBr plates. The UV spectra were taken on an SV-8 spectrophotometer.

Reaction of (I) with Aniline. To a stirred solution of 10 g of (I) in 50 ml of absolute benzene at 20° was added 2.5 g of aniline and the mixture was stirred at 20-22° for 1 h. The solution was filtered, the solvent was vacuum distilled, and the residual viscous oil was treated with 50 ml of 20% aqueous KOH solution. The obtained precipitate was filtered, washed with a little water, and recrystallized from water. We obtained 5.3 g (93%) of 1,6-dimethyl-N^7-phenylcytosine [2], mp 299-300°. Found: C 67.45; H 6.15; N 20.07%. $C_{12}H_{13}ON_3$. Calculated: C 67.00; H 6.05; N 19.57%.

Reaction of (I) with Diethylamine. To a solution of 13.3 g of (I) in 50 ml of absolute benzene at 20° was added 2.9 g of Et_2NH. After 20 min the mass was filtered (filtrate A), and the residue on the filter was boiled in 50 ml of benzene and filtered (filtrate B). The insoluble residue was recrystallized from n-propanol. We obtained 1.3 g (26%) of 1,6-dimethyluracil [3], mp 220-222°. Filtrate B was evaporated in vacuo, and the residual solid was recrystallized from benzene. We obtained 7.8 g (68%) of diethylamine diphenyl phosphate, mp 124-126°. Infrared spectrum (ν, cm^{-1}): 2500, 2680—2900 ($\overset{+}{N}H-H$), 915, 1100, 1220, 1270 ($\geq P(O)O^-$), 1595 (C_6H_5). Filtrate A was evaporated in vacuo, the residue was treated with a mixture of benzene and petroleum ether (70-100°), and the insoluble residue was filtered (filtrate C) and then recrystallized from a benzene—petroleum ether mixture. We obtained 4.85 g (70%) of 1,6-dimethyl-N^7,N^7-diethylcytosine, mp 142-143°. Infrared spectrum (ν, cm^{-1}): 1620—1640 (C=O). Ultraviolet spectrum (λ_{max}, nm): 289 (0.1 N HCl). Found: C 61.57; H 8.70; N 22.10%. $C_{10}H_{17}N_3O$. Calculated: C 61.50; H 8.72; N 21.48%. Filtrate C was evaporated in vacuo. We obtained 2.9 g (28%) of diphenyl N,N-diethylamidophosphate [4], mp 60-61°.

Reaction of (I) with N-(o-tolyl)piperazine. To a solution of 26.6 g of (I) in 70 ml of absolute benzene at 25° was added a solution of 12.2 g of N-(o-tolyl)piperazine in 30 ml of absolute benzene and the mixture was stirred for 1 h. The mass was filtered, and the precipitate was washed with benzene, dried, and recrystallized from n-propanol. We obtained 6.3 g (63%) of 1,6-dimethyluracil. The filtrate was evaporated in vacuo, and the residual oil was treated with 50 ml of 20% KOH solution and then immediately extracted with benzene (3 × 50 ml). The benzene extracts were dried over Na_2SO_4, filtered, and evaporated in vacuo. The residual oil was treated with ether. The obtained precipitate was filtered (filtrate A), washed with ether, and recrystallized from a benzene—petroleum ether mixture. We obtained 7.35 g (34.7%) of 1,6-dimethyl-4-[N-(o-tolyl)-N'-piperazinyl]cytosine, mp 181-182°. Infrared spectrum (ν, cm^{-1}): 1635 (C=O). Ultraviolet spectrum (λ_{max}, nm): 290 (0.1 N HCl). Found: C 68.50; H 7.89; N 18.47%. $C_{17}H_{24}N_4O$. Calculated: C 68.00; H 8.00; N 18.67%. From filtrate A we obtained 18.6 g (63.8%) of diphenyl N-[N-(o-tolyl)-N'-piperazinyl]amidophosphate as a viscous oil. Infrared spectrum (ν, cm^{-1}): 1197 (P—O—C_6H_5), 1230 (P=O), 1600 (C_6H_5). Found: C 67.10; H 6.20; N 6.49; P 7.80%. $C_{23}H_{26}N_2O_3P$. Calculated: C 67.50; H 6.35; N 6.86; P 7.58%.

Reaction of (I) with NH_3. A gentle stream of dry NH_3 was passed through a solution of 14.3 g of (I) in 100 ml of absolute benzene for 30 min at 25°. The obtained precipitate was filtered, washed with benzene, and treated with ethanol (25°). The insoluble residue was filtered, and then recrystallized from ethanol. We obtained 5.2 g (96.5%) of 1,6-dimethyluracil. The mother liquor was evaporated, and the residue was recrystallized from $CHCl_3$. We obtained 9.32 g (97.3%) of diphenyl amidophosphate [5], mp 148-149°.

Reaction of (II) with Aniline. To a solution of 2.42 g of (II) in 50 ml of absolute benzene at 25° was added 0.38 g of aniline and the mixture was stirred for 1 h. The solvent was removed in vacuo, and the residual oil was treated with 20% KOH solution until neutral and immediately extracted with benzene (3 × 50 ml). The benzene extracts were dried over Na_2SO_4, filtered, and evaporated in vacuo. We obtained

1.69 g of an oil that was transferred to an Al_2O_3 column and washed in succession with petroleum ether, benzene, and n-propanol. From the fraction eluted with propanol we obtained 1.25 g (69%) of 1-[ω-(dibutylphosphono)butyl]-N^7-phenylcytosine as a viscous oil. Infrared spectrum (ν, cm^{-1}): 1680 (C=O), 3100–3300 (N–H), 1240 (P=O), 1005, 1025, 1070 (P–O–C). Ultraviolet spectrum (λ_{max}, nm): 295 (0.1 N HCl). Found: N 9.87; P 7.07%. $C_{22}H_{34}N_3O_4P$. Calculated: N 9.66; P 7.13%.

Reaction of (IV) with Aniline. To a solution of 5 g of (IV) in 50 ml of absolute benzene at 25° was added 1.25 g of aniline. After 1 h the obtained precipitate was filtered, washed with benzene, and dried in vacuo. We obtained 5.4 g (86.5%) of 2-phenylamino-3,6-dimethyl-3,4-dihydro-4-pyrimidone (V) diphenyl phosphate. The salt was dissolved by heating in 50 ml of 20% KOH solution. The precipitate obtained on cooling was filtered and recrystallized from n-propanol. We obtained 2.1 g (73.5%) of (V), mp 195-200°. Infrared spectrum (ν, cm^{-1}): 1670 (C=O), 3345 (N–H). Ultraviolet spectrum (λ_{max}, nm): 255 (0.1 N HCl). Found: C 66.80; H 5.93; N 19.71%. $C_{12}H_{13}N_3O$. Calculated: C 66.98; H 6.05; N 19.53%.

Reaction of (VI) with Aniline. To a solution of 3.8 g of (VI) in 50 ml of absolute benzene at 25° was added 0.95 g of aniline. After 1 h the obtained precipitate was filtered, washed with benzene, and treated with 200 ml of n-propanol (40°). The insoluble residue was filtered (filtrate A), and then recrystallized from n-propanol. We obtained 1.2 g (84%) of 3,6-dimethyluracil [3], mp 260-262°. The solid residue obtained from the evaporation of filtrate A was recrystallized from n-propanol. We obtained 2.8 g (83.5%) of diphenyl N-phenylamidophosphate [6], mp 129°.

Reaction of (VI) with Diethylamine. To a solution of 2.2 g of (VI) in 50 ml of absolute benzene at 25° was added 1.1 g of Et_2NH. After 1 h the obtained precipitate was filtered, washed with benzene, and then boiled with 100 ml of benzene and the insoluble residue was filtered. The residue was recrystallized from n-propanol. We obtained 0.7 g (84.5%) of 3.6-dimethyluracil, mp 261-262°. The benzene extract was evaporated in vacuo, and the residue was recrystallized from benzene. We obtained 1.5 g (88.2%) of diphenyl N,N-diethylamidophosphate, mp 59-61°.

Reaction of Esters (VII) and (VIII) with Aniline. To a solution of 3.6 g of mixed esters (VII) and (VIII), which, based on the ^{31}P-NMR spectral data, contained 70% of ester (VII), in 50 ml of absolute benzene at 25° was added 0.58 g of aniline. After 1 h the obtained precipitate was filtered and recrystallized from n-propanol. We obtained 1.3 g (64.8%) of diphenyl N-phenylamidophosphate, mp 128-129°. The filtrate was evaporated in vacuo, the residual oil was treated with 20% KOH solution until neutral, and the mixture was extracted with benzene (3 × 50 ml). The benzene extract was dried over Na_2SO_4, filtered, and evaporated in vacuo. The residual oil was transferred to an Al_2O_3 column and washed in succession with petroleum ether, diethyl ether, benzene, n-propanol, and methanol. From the benzene–propanol fractions we obtained 0.43 g (28.2%) of (XI) as a viscous oil. Infrared spectrum (ν, cm^{-1}): 1660 (C = O), 3100–3300 (N–H), 1220–1240 (P = O), 990–1070 (P–O–C). Ultraviolet spectrum (λ_{max}, nm): 258 (0.1 N HCl). Found: N 9.73; P 7.53%. $C_{21}H_{32}N_3O_4P$. Calculated: N 9.96: P 7.37%. From the n-propanol–methanol fractions we isolated 1.38 g (61.5%) of (IX), which in its IR spectrum was completely identical with the spectrum that was obtained as described in [7].

CONCLUSIONS

The isomeric diphenyl uracil phosphates react with amines either at the phosphorus atom or at the carbon atom of the pyrimidine ring, depending on the position of the substituent on either the N^1 or N^3 atoms of the ring, the position of the diphenylphosphonoxy group, and the nature of the amine.

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