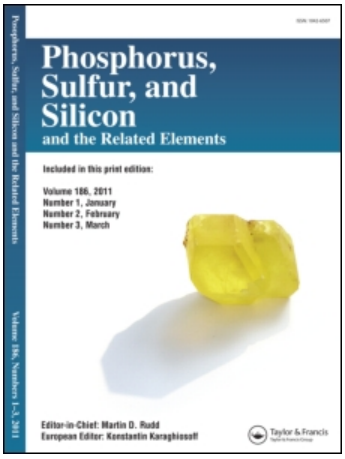

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REACTIONS OF URACILS WITH TRIALKYL PHOSPHITES AND DIALKYL PHOSPHONATES

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2-Thiouracil (**1**) reacts with TAP (**5**a,b) to give the respective 1,3-dialkyl derivatives **2** along with the monophosphonates **10**, **11** and **15**. On the other hand, component **2**a reacts with **5**a and **5**b to give one and the same product, proved to be dithiouracil **22**. 5-Nitrouracil (**3**) reacts with **5** by a different pathway to give mainly the new pyrimidines **27** (major) and the alkylated derivatives **4**a,b (minor). Reactions of **1** and **3** with DAP (**6**a,b), proceed, only in the presence of p-TsOH to give the monophosphonates **15** and **28**, respectively.

Keywords: Uracils; alkyl phosphites; heterocyclic-phosphonates; dithiouracils; nitro group-deoxygenation by trialkyl phosphites

INTRODUCTION

Research into organophosphorus compounds has steadily flourished because many organophosphorus compounds have been reported to possess antibacterial, antibiotic, antineoplastic or antiviral activity.[1] For this reason, the synthesis of phosphorus-substituted heterocycles was extensively studied by us.[2–6] Phosphono-substituted pyrimidines in general, and -uracils, in particular, should be of an interest, since numerous uracils possess a wide spectrum of biological/pharmacological activities and several derivatives are in clinical use.[7–10] The objective of this study was to investigate the interaction of 2-thiouracil (**1**) and 5-nitrouracil (**3**) as well as their 1,3-dialkylated derivatives **2**a and **4**a, respectively, with alkyl phosphites of type **5**a,b and dialkyl phosphonates of type **6**a,b.

Uracils are examples of 6-membered ambident heterocyclics possessing several tautomeric structures (eq. 1) and display dual reactivity.[11] Nevertheless, it

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has been established that the preference of these compounds exists in the lactam structure over the lactim form.[12,13]

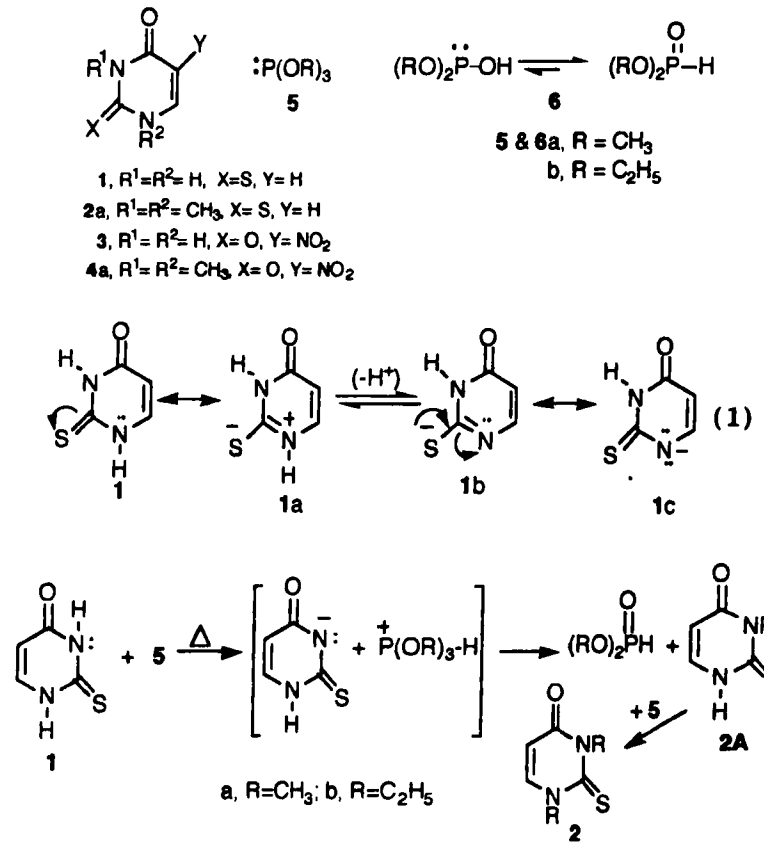
RESULTS AND DISCUSSION

I. Reaction of 1 and 2a with TAP (5a,b)

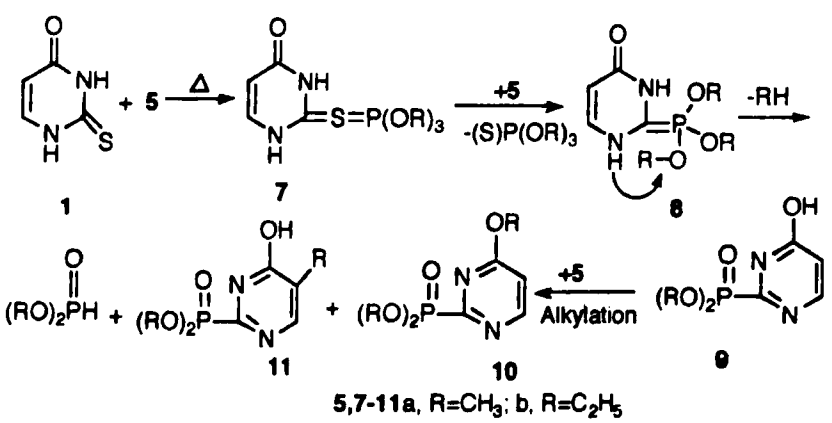
The reaction of 2-thiouracil (**1**) and excess of trimethyl phosphite (**5**a), employed as a solvent, was completed after heating at 105°C for ~ 18 h (TLC). Examination of the product mixture prior to workup by ^{31}P NMR spectroscopy indicated the presence of three phosphonate products (positive ^{31}P shifts around 29.6 ppm as well as a signal at 74.1 ppm attributed to trimethyl thiophosphate). These data rule out formation of any alternative phosphorothioate constitution. The product mixture was then subjected to column chromatography to afford colorless crystals of the known[14] 1,3-dimethyl-2-thiouracil (**2**a) (17.8%, Scheme 1), along with the monophosphonates **10**a, **11**a (Scheme 2) and **15**a (Scheme 3).

Compound **10**a (24%, δp = 29.2 ppm) was formulated as dimethyl (4-methoxy-1,3-pyrimidine-2-yl) phosphonate based upon: (a) the elemental analysis and molecular weight determination (MS) correspond to $C_7H_{11}N_2O_4P$ (218.15); (b) the bands due to the amidic- and the thioamidic carbonyl groups present in the infrared spectrum of **1** at cm^{-1} 1687 and 1424, respectively, were absent in the IR spectrum of **10**a. However, characteristic absorption bands were observed at 1078 (P-O-C) and 1265 (P=O, free). In addition, the spectrum did not exhibit any -NH or -OH band in 3450-3300 region; (c) the ^1H NMR of **10**a disclosed a doublet ($^3J_{HP}$ = 9.3 Hz) centered at 3.97 ppm for the two (OCH_3) groups attached to phosphorus, while the C-4-methoxyl protons appeared as a singlet at 3.72 ppm. Moreover, the two doublets (each with $^2J_{HH}$ = 3.8 Hz) at 5.84 and 7.4 assignable to the two protons on C-5 : C-6 ethylene in **1** are still present at the same PMR range of **10**a. These assignments are also supported by ^{13}C NMR[15,16] which gave a doublet (J_{CP} = 122.3 Hz) at δ_C = 148.4 (C-P) and at 54.2 ppm (P-O-C, d, J_{CP} = 7.3 Hz), among others.

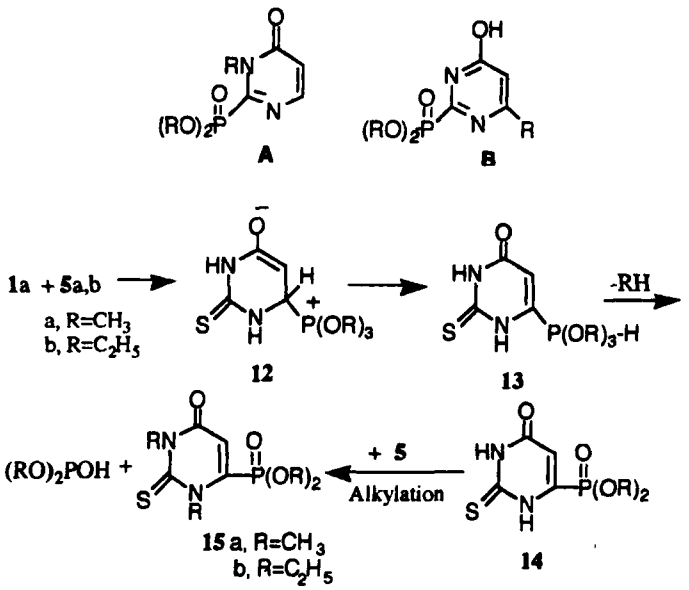
Component **11**a (13.2%, δ_p = 29.8 ppm) was found to be an isomer ($C_7H_{11}N_2O_4P$) (218.15) but not identical with structure **10**a and assigned dimethyl (5-methyl-4-hydroxy-1,3-pyrimidine-2-yl) phosphonate for the following reasons: (a) its infrared spectrum revealed the characteristic absorption bands attributable to the stretching frequencies of OH (3435), P=O (1237) and P-O-C (1063) cm^{-1} functions; (b) the ^1H NMR spectrum of **11**a showed protons of the



SCHEME 1



SCHEME 2



SCHEME 3

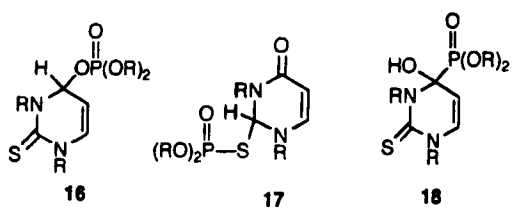
C_5-CH_3 as a singlet at 2.03 and the hydroxyl proton at 10.6 ppm. On the other hand, the ethylenic protons (2H, C_5-**H**: C_6-**H**, 2d) present in the PMR spectrum of **1** and **10**a at ~5.84 and ~7.4 were absent in the spectrum of **11**a. Instead, only a singlet appeared at 6.82 ppm; (c) the ^{13}C NMR spectrum was also in accord with the proposed structure, e.g., the substituted methyl signal appeared at δ_C = 25.6 ppm. However, the data of the methyl group and the lack of the AB system in the PMR of **11**a, as well as the absence of amidic carbonyl group in its IR and ^{13}C NMR spectra confirm the assigned structure and rule out other alternative structures like **A** and **B**.

The third monophosphonate product **15**a (δ_P = 30.4 ppm) was obtained in 9.6% yield and formulated as dimethyl (1,3-dimethyl-4-oxo-2-thiouracil-6-yl) phosphonate. The structural assignment for **15**a is based upon: (a) its elemental and mass spectral analyses corresponded to an emperical formula $C_8H_{13}N_2O_4PS$ (264.24); (b) in the IR spectrum of **15**a, the absorption bands observed at υ 1690 and 1445 cm^{-1} were assigned to the amidic and thioamidic carbonyl functions, respectively; (c) the ^1H NMR of **15**a revealed the presence of signals at 3.35 (3H, N_1-CH_3, d, $^4J_{HP}$ = 4.2 Hz), 3.52 (3H, N_3-CH_3, s), while the two methoxyl groups attached to the phosphorus atom appeared as two doublets (6H, each with $^3J_{HP}$ = 10.3 Hz) at 3.94 and 4.1 ppm. This splitting is probably due to the asymmetry of the molecule.[17] The C_5-methine proton appeared as a doublet

($^3J_{HP}$ = 10.3 Hz) at 6.15 ppm; (d) the ^{13}C NMR data are: δ_C 38.3 (N_1-CH_3, d). 39.1 (N_3-CH_3, s), 51.1 and 52.8 (OCH_3, 2d, J_{CP} = 7.3 Hz), 128.6 (C_5-H, d, J_{CP} = 7.3 Hz), 141.7 (C-P, d, J_{CP} = 133.5 Hz), 165.4 (C=O) and 181.6 (C=S). Further structural proof of **15**a was provided by subjecting **15**a to thermolysis under reduced pressure whereby the parent dimethyl-2-thiouracil (**2**a) along with dimethyl phosphonate (**6**a) were, as expected, regenerated and identified (eq. 2). On the basis of the aforementioned analytical and spectroscopic arguments,

$$15a \xrightarrow[5\ mm/Hg]{\Delta\ 250C/} 2a + \underset{6a}{DMP} \qquad (2)$$

structure **15**a is more consistent than the other possible structures of type **16**, **17** or **18**.



Parallel compounds **2**b, **10**b, **11**b and **15**b (b, R=C_2H_5) were likewise obtained by reacting **1** with triethyl phosphite (**5**b) under the conditions previously mentioned with **5**a. The identification of the products was confirmed by combustion analysis, mass and NMR spectroscopy as well as by analogy with **10**a, **11**a and **15**a.

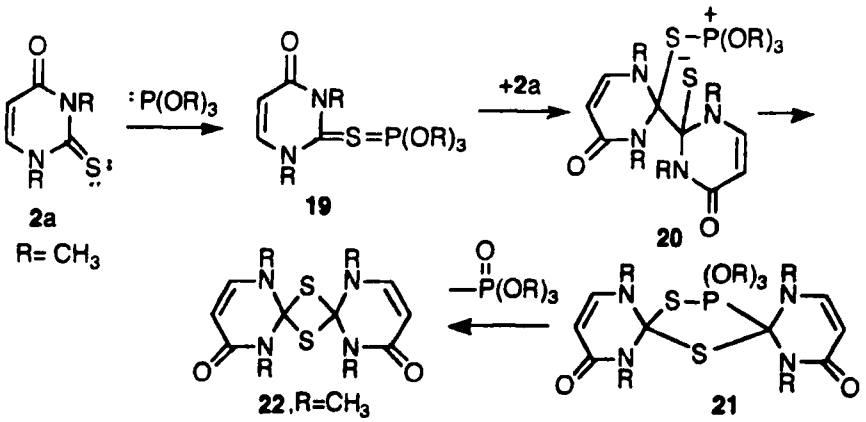
Schemes 1–3 show the mechanisms for the interaction of trialkyl phosphites (**5**a,b) with 2-thiouracil, which are consistent with the data presented thus far. However, the structural products **2**, **10**, **11** and **15** indicated, besides the N-alkylation, that two positions in **1** are susceptible to nucleophilic attack: the thioamide group and the α,β-unsaturated carbonyl system in **1**. A possible mechanism for the formation of N-alkylation processes is depicted in Scheme 1. This is based on direct attack by the anionic centre in **1** on the alkoxyalkyl group of the reagent **5** to give mono-N-alkylation product **2**A which is subsequently N-alkylated in an identical way to give 1,3-dialkylated-2-thiouracil (**2**).

Next, the attack on the thioamide group in **1** by **5** will be considered. The initial thiophilic addition is assumed[18] in many other reactions involving nucleophilic reagents with thioamides, and it is not unreasonable to believe that thiouracil might act in the same manner as thioamides since from its spectral studies,[11,19] it has a structure and reactions completely analogous to thioamides. Following this[20], the addition of **5** on **1** leads to the reactive intermediate **7** which reacts further with a second equivalent of trialkyl phosphite (**5**) to give the desulfurized ylide **8** accompanied by trialkyl thiophosphate extrusion. Stabilization of **8** could be attained by formation of the $-P=O$ bond *via* the loss of RH moiety. The parallel alkylation of **9** by **5** (Scheme 1) affords either **O**-alkylated product **10** or C_5-alkylpyrimidine **11**. However, formation of **11** could be considered as a result of intramolecular reaction of **10** (*ortho*-Claisen rearrangement)[21] proceeding through a six-membered cyclic transition state. Minnemeyer[21] reported the application of the *ortho* Claisen rearrangement to the pyrimidine ring system.

On the other hand, the formation of the monophosphonates **15** could be rationalized in terms of the carbophilic attack by the phosphite-phosphorus on C_6-in the α,β-unsaturated system, concurrently to the formation of the phosphorothioate intermediate **7**, to give the dipolar form **12** (Scheme 3), which occurs *via* 1:4 addition. Stabilization of **12** by formation of the -P=O bond and elemination of RH moiety afforded **14** *via* **13**. The parallel N-alkylation (*cf.* Scheme 1) led to the formation of **15**.

It should be noted that, the hypothesis that **15** could result from further reaction of **2** with **5** can not be overlooked. However, isolation of **2**, **10**, **11** and **15** from the above reaction can be explained in terms of the propensity of this class of compounds (uracils) to be N-alkylated. Alkylation predominates over all the other competing reactions of **1** with **5**. Thus, it is obvious that the first stage (phosphorylation) of the reaction is much faster than the second (alkylation), so that the latter does not interfere with the kinetics of the former.

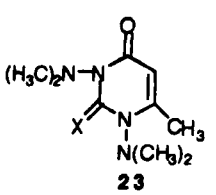
We have therefore investigated the reaction of the dialkyl component **2**a (as a representative example) with trialkyl phosphites (**5**a,b), using the same reaction conditions. As expected, the reaction was found to proceed by a very different route (Scheme 4) leading mainly to the formation of **22** (62%). On the other hand, compound **15a** (<5%) was identified in the product mixture (with **5a**, TLC). Although the free disulfide of 2-thiouracil, previously reported[22] is too unstable, the dithione **22** was found to be stable at normal conditions. In support of the assigned structure **22**, its mass spectrum gave a prominent ion peak at 312 (M^+, 50%) while the elemental and spectroscopic data afforded the features of the parent monomeric thione **2**a. We believe the series of transformations outlined in Scheme 4 is involved in the formation of the observed dithione **22**.



SCHEME 4

Following Scherowsky[23], and Corey[24], the intermediate **19** is the first species formed in reactions of this sort. Formation of **22** requires the cojoining of **19** with a second equivalent of uracil species **2a**, suggesting they might react by [3 + 2] dipolar addition, to give the betaine **20**, the intermediate **20**, represented by a heterocyclic structure **21** is expected to lose $P(OR)_3$ as $O{=}P(OR)_3$ as a result of its oxidation by the adventitious H_2O, the remainder, in turn, could easily transformed into the observed dithione **22**.

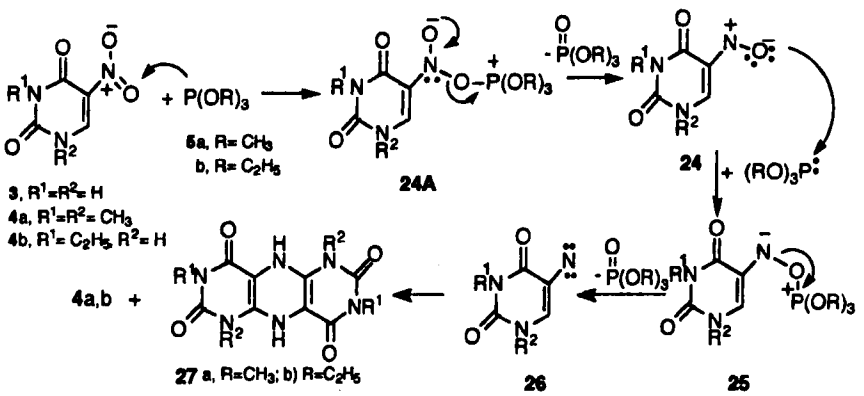
Remarkably, it has previously been reported that uracils of type **1** (X=O, S) are converted by hexamethylphosphoryltriamide into 1,3-(bis-dimethylamino)-6-methylpyrimidine (**23**) in 70% yield. The parallel trialkylated compound has not hitherto been observed.



23

II. Reactions of Uracils 3 and 4a with TAP (5a,b)

We have now investigated the reaction of 5-nitrouracil (**3**) with excess trimethyl- (**5a**) and triethyl phosphite (**5b**) and find no evidence for any significant production of phosphorylated product (^{31}P NMR). However, chromatography led to the isolation of a pure sample of the major product (**27a**) or (**27b**) (Scheme 5). It was interesting to note that a substantial quantity of 1,3-dimethyl-5-nitrouracil (**4a**) was also isolated in the first reaction with **5a**, meanwhile, in the latter reaction



SCHEME 5

(with **5**b), only monoethylated substrate (**4**b) was obtained, suggesting that, likewise with **1**, the alkylation process predominates over all other possible reactions. Structure **27** is consistent with the spectroscopic data available (see experimental).

The formation of the pyrimidine **27** can be rationalized by the generally accepted mechanism of nucleophilic attack by the phosphite-phosphorus on an oxygen of the nitro group in **3** to give a nitroso-intermediate **24** *via* the betaine species **24A**. Subsequent deoxygenation in an identical way affords the reactive nitrene **26**, which can be trapped by a second equivalent of **26** to give **27**. Obviously, alkylation processes compete with these transformations (Scheme 5) which ultimately yielded the final products. The deoxygenation of nitro and nitroso compounds by trialkyl phosphites and (less readily) by phosphines has attracted considerable attention of many investigators.[26]

Furthermore, this study has been extended to include the reaction of 1,3-dimethyl-5-nitrouracil (**4**a) with the same phosphite reagents to establish whether it would behave in a similar manner. We have found that compound **4**a reacts with **5**a or **5**b under the same conditions to give, in both reactions, the same pyrimidine **27**a in ~70% yield. No phosphorylated products were observed.

III. Reaction of 1 and 3 with Dialkyl Phosphonates (6a,b)

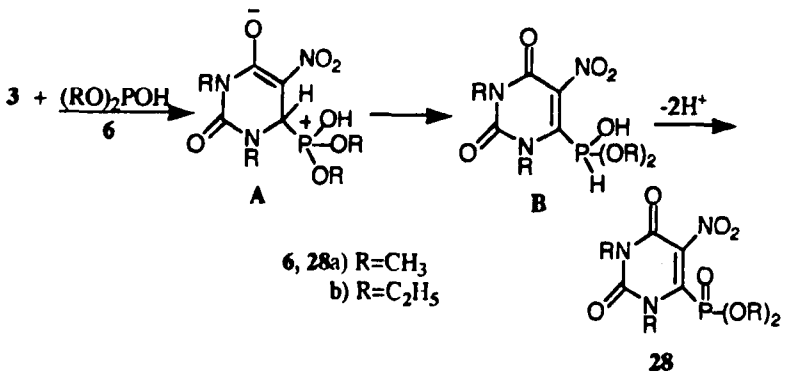
Efforts were made to prepare some phosphorylated derivatives from 5-nitrouracil. This was achieved by allowing the appropriate dialkyl phosphonates (**6**a) or (**6**b) to react with the substrate **3** in absence of solvent at 100 °C for 22 h to give the monophosphonate **28**a or **28**b, respectively, in a good yield. This

reaction proceeded only when a trace amount of p-toluenesulfonic acid (p-TsOH) was present in the medium. The new phosphonates **28** were compatible with analytical and spectroscopic data.

Moreover, in the same way, 2-thiouracil (**1**) reacted with the dialkyl phosphonates (**6**a,b) in the presence of p-toluenesulfonic acid to give the monophosphonate **15**a or **15**b, respectively, (eq. 3).

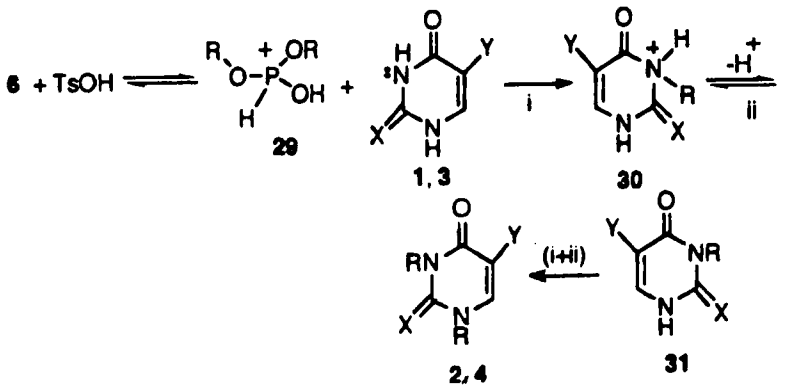
$$\mathbf{1} + \underset{\mathbf{6}}{(RO)_2POH} \xrightarrow{p\text{-TsOH}} \mathbf{15a,b} \qquad (3)$$

A possible mechanism for the aforementioned N-alkylation process which proceeds only in the presence of a protonating agent (p-TsOH) could be explained in terms of the initial protonation of the dialkyl phosphonate by p-TsOH to afford the phosphonium species **29**. Nucleophilic attack by nitrogen in **3** on the protonated-DAP **29** affords cation **30** which then releases a proton to afford **31** followed by another alkylation process to afford **2** or **4** (Scheme 7). On the other hand, we presume that the phosphorylation of **1** and **3** with DAP proceeds in parallel with its alkylation to give the intermediate species **28**A which then releases two protons to afford **28** (Scheme 6).



SCHEME 6

Data on the biological activity of the new compounds **10**, **11**, **15**, **22**, **27** and **28** will be published elsewhere.



SCHEME 7

CONCLUSION

As a sequel of the present study, it could be concluded that the tautomeric structures and proton mobility in these pyrimidines (uracils) (*cf.* **1–1c**) should be considered to be at least as important as the steric factors. However, the feature common to all of the isolated products from these reactions of alkyl phosphites and uracils **1** and **3** is along the lines which have been previously explored[11,12] for the tendency of these pyrimidines to be N-alkylated, particularly, in the lactam form rather the lactim structure. The results also show a marked resemblance between **1** and **3** in their chemical behavior toward DAP under similar conditions to give the phosphonates **15** and **28**, respectively; meanwhile they behave differently toward trialkyl phosphites. Thus, while the initial nucleophilic attack by TAP was mainly on the sulfur atom in **1** to give the phosphonates **10** and **11**, a reduction pathway for the nitro group was assumed to be the first step in the reaction of **3** and **5**. Furthermore, the findings clearly indicate that the behavior of alkylated uracils **2**, which are locked in the lactam form by the presence of substituents on nitrogen atoms, is in marked disparity with the behavior of the parent **1** toward the same reagents whereby the dithione **22** was the major product from the first reaction and the mono-phosphonates **10**, **11** and **15** were the reaction products of the other one.

Finally, this successful application of the TAP and DAP to induce N-alkylation (*cf.* **2** and **4**) contributes to their potential as alkylating agents for acids, alcohols, phenols and thiols.[27]

EXPERIMENTAL

All melting points were uncorrected. The IR spectra were obtained with a Phillips Infracord Spectrometer Model PU 9712 in KBr discs. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ or d_6-DMSO as solvents on a Joel-270 MHz Spectrometer and the chemical shifts were recorded in δ ppm relative to TMS. The ^{31}P NMR spectra were taken with a Varian CFT-20 (*vs.* external 85% H_3PO_4). Mass spectra were performed at 70 eV on a Shimadzu GCS-QP 1000 EX Spectrometer provided with a data system. The appropriate precautions in handling moisture-sensitive compounds were observed. Solvents were dried by standard techniques.

Reaction of 2-thiouracil (1) *with trimethyl phosphite* (5a)

General Procedure: A mixture of **1** (1.3 g, 0.01 mol) and **5a** (5 ml) was heated at 105°C for ~18 h. After evaporation of the volatile materials, *in vacuo*, the residual substance was treated with ethanol (100 ml) and evaporated to dryness in the presence of silica gel (7 g). The mixture was then added to a column, previously charged with silica gel in light petroleum (b.r., 60–80 °C). The column was eluted with light petroleum containing increasing amounts of chloroform and then with pure ethyl acetate to give the following components in sequence:

1) Elution with 100% light petroleum afforded a colorless substance (277 mg, 17.8%), m.p. 109–110 °C (ethanol-diethyl ether, 1:1 v/v) and proved to be 1,3-dimethyl-2-thiouracil (**2a**) (m.p., mixed mp and comparative IR and MS spectra).[14]
2) Fraction up to 1:1 v/v eluted a colorless substance of dimethyl (1,3-dimethyl-2-thiouracil-6-yl) phosphonate (**15a**) (255 mg, 9.6%), a m.p. 121–123 °C (acetone). Anal. Calcd. for: $C_8H_{13}N_2O_4PS$ (264.24): C, 36.36; H, 4.96; N, 10.6; P, 11.72; S, 12.13. Found: C, 36.13; H, 4.94; N, 10.28; P, 11.84; S, 12.01%. IR (KBr) cm^{-1}: 1690 (C=O), 1622 (C=C), 1445 (C=S), 1235 (P=O), 1100 (P-O-C). NMR ($CDCl_3/CD_3OD$) δ_H ppm: 3.35 (3H, N_1-CH_3, d, $^4J_{HP}$ = 4.21 Hz), 3.52 (3H, N_3-CH_3, s), 3.94, 4.1 (6H, P-O-CH_3, 2d, $^3J_{HP}$ = 10.3 Hz), 6.15 (1H, C_5-**H**, d, $^3J_{HP}$ = 10.3 Hz). δ_C: 38.3 (N_1-CH_3, d, $^3J_{CP}$ = 4.8 Hz), 39.1 (N_3-CH_3, s), 51.1, 52.8 (P-O-CH_3), 2d, J_{CP} = 7.3 Hz), 128.6 (C_5-H, d, $^3J_{CP}$ = 7.3 Hz), 141.7 (C-P, d, J_{CP} = 133.5 Hz), 165.4 (C=O), 181.6 (C=S); δ_p = 30.4 ppm. MS: m/z = 264 (M^+, 12%). Elution with pure chloroform afforded a pale yellow substance of dimethyl-(4-

methoxy-1,3-pyrimidine-2-yl) phosphonate (**10**a) (523 mg, 24%), m.p. 137–139 °C (CH_3OH-cyclohexane, 2:1 v/v). Anal. Calcd. for $C_7H_{11}N_2O_4P$ (218.15): C, 38.54; H, 5.08; N, 12.84; P, 14.2. Found: C, 38.28; H, 4.83; N, 12.71; P, 14.36%. IR (KBr) cm^{-1}: 1627 (C=C), 1265 (P=O), 1078 (P-O-C). NMR (d_6-DMSO), δ_H, ppm: 3.72 (3H, C-O-C**H**$_3$, s), 3.97 (6H, P-O-C**H**$_3$, d, $^3J_{HP}$ = 9.3 Hz), 5.88 (1H, -C_5-**H**, d, J_{HH} = 3.8 Hz), 7.36 (1H, -C_6-**H**, d, J_{HH} = 3.8 Hz); δ_C ppm: 50.4 (C-O-CH_3), 54.2 (P-O-CH_3, d, $^3J_{CP}$ = 7.3 Hz), 132.8 (C_5-H), 144.6 (C_6-H), 148.4 (N=C-P, d, J_{CP} = 122 Hz), 158.8 (C-O-CH_3); δ_P = 29.2 ppm. MS: m/z = 218 (M^+, 18%).

Elution with pure ethyl acetate yielded dimethyl (5-methyl-4-hydroxy-1,3-pyrimidine-2-yl)phosphonate (**11**a) as pale yellow crystals (285 mg, 13.2%) m.p. 168–170 °C (chloroform). Anal. Calcd for $C_7H_{11}N_2O_4P$ (218.15): C, 38.54; H, 5.08; N, 12.84; P, 14.2. Found: C, 38.37; H, 4.82; N, 12.69; P, 13.95. IR: (KBr) cm^{-1}: 3435 (OH), 1610-1580 (C=C and C=N), 1237 (P=O), 1063 (P-O-C). NMR ($CDCl_3/CD_3OD$). δ_H ppm: 2.03 (3H, C_5-C**H**$_3$, s), 3.98 (6H, P-O-C**H**$_3$, d, $^3J_{HP}$ = 9.3 Hz), 6.82 (1H, C_6-**H**, s), 10.6 (1H, -**OH**, s); δ_C ppm: 25.6 (C_5-CH_3), 53.6 (P-O-CH_3, d, $^3J_{CP}$ = 7.3 Hz), 132.8 (C_6-H), 147.6 (N=C-P, d, J_{CP} = 122.3 Hz), 155.3 (C-OH); δ_P = 29.8 ppm. MS: m/z = 218 (M^+, 35%).

The ^{31}P NMR spectrum of the product mixture (**1** + **5**a) prior to workup had six strong peaks at δ_P = 140.3 (unreacted **5**a), 74.2 [$(MeO)_3P(S)$], 29.2 (**10**a), 29.8 (**11**a), 30.4 (**15**a) and 4.5 ppm [$(MeO)_3P(O)$], from air-oxidation of the TMP and some unidentified resonances.

Reaction of **1** *and* **5b**

Reaction of **1** with triethyl phosphite (**5b**) was carried out in the absence of solvent, similar to the general procedure, using the same amounts. After evaporation of the volatile materials in *vacuo*, **15**b, **2**b, **10**b, and **11**b were obtained, respectively, by column chromatography (silica gel/light petroleum (b.r., 60–80 °C) with increasing amounts of chloroform.

Diethyl (1,3-diethyl-2-thiouracil-6-yl) phosphonate (**15**b), colorless crystals (374 mg, 11.7%),[a]Yield of **15**b based on the starting material **1** mp. 48–50 °C (EtOH-pentane, 1:2 v/v). Anal. Calcd. for: $C_{12}H_{21}N_2O_4PS$ (320.35): C, 44.99; H, 6.6; N, 8.74; P, 9.67; S, 10.0. Found: C, 44.84; H, 6.44; N, 8.53; P, 9.39; S, 9.87%. IR (KBr) cm^{-1}: 1685 (C=O), 1610 (C=C), 1461 (C=S), 1243 (P=O), 1038 (P-O-C). NMR (d_6-DMSO)[b] δ_H ppm: 0.7, 1.3 (12H, -CH_2-C**H**$_3$, 2m), 3.3–4.12 (8H, -C**H**$_2$-CH_3, m), 6.6 (1H, C5-**H**, d, $^3J_{HP}$ = 10.5 Hz). δ_H = 26.6 ppm. Ms: m/z = 320 (M^+, 21%).

1,3-Diethyl-2-thiouracil (**2b**), colorless crystals (396 mg, 22%), mp. 64–66 °C (diethyl ether) (mp., mixed mps and comparative IR and MS spectra).[14]

Diethyl (4-ethoxy-1,3-pyrimidine-2-yl) phosphonate (**10b**), pale yellow crystals (680 mg, 26.2%), mp. 87–89 °C (CH_2Cl_2). Anal. Calcd. for $C_{10}H_{17}N_2O_4P$ (260.23): C, 46.15; H, 6.58; N, 10.76; P, 11.9. Found: C, 45.82; H, 6.37; N, 10.54; P, 11.76%. IR (KBr) cm^{-1}: 1622 (C=C), 1255 (P=O), 1030 (P-O-C). NMR (DMSO-d_6), δ_H ppm: 0.4–1.4 (9H, OCH_2-C**H**$_3$, 2m), 3.51 (2H, OC**H**$_2$, q), 3.97 (4H, P-O-C**H**$_2$, qt), 6.16 (1H, C_5-**H**, d, J_{HH} = 3.8 Hz), 8.2 (1H, C_6-**H**, d, J_{HH} = 3.8 Hz). δ_C ppm: 17.6, 18.8 (O-C-**C**H$_3$, 2t), 56.2–58.3 (C-O-**C**H$_2$ & P-O-**C**H$_2$-, 2q), 143.6 (**C**-P, d, J_{CP} = 122.3 Hz), 152.7 (**C**-O-CH_3): δ_P = 28.6 ppm. MS: m/z = 260 (M^+, 18%).

Diethyl (5-ethyl-4-hydroxy-1,3-pyrimidine-2-yl) phosphonate (**11b**) (373 mg, 14.4%), mp. 102–104 °C (acetonitrile). Anal. Calcd. for: $C_{10}H_{17}N_2O_4P$ (260.23): C, 46.15; H, 6.58; N, 10.76; P, 11.9. Found: C, 45.88; H, 6.43; N, 10.61; P, 11.73%. IR (KBr) cm^{-1}: 1620 (C=C), 1250 (P=O), 1028 (P-O-C). NMR (DMSO-d_6): δ_H ppm: 0.5 (3H, C_5-CH_2-C**H**$_3$ t), 0.8 (6H, P-O-C-C**H**$_3$, d of t, J_{HH} = 4 Hz, $^3J_{HP}$ = 10.5 Hz), 2.58 (2H, C-C**H**$_2$-C, q, J_{HH} = 4 Hz), 3.95 (4H, P-O-C**H**$_2$, qt), 7.4 (1H, C_6-**H**, s), 10.1 (1H, O**H**, br.); δ_C ppm: 11.2 (C-C-**C**H$_3$), 17.3 (P-O-C-**C**H$_3$, d), 21.5 (C-**C**H$_2$-C, s), 59.9 (P-O-**C**H$_2$, d), 131.9 (**C**$_6$-H, s), 142.6 (N=**C**-P, d, J_{CP} = 122.5 Hz), 159.5 (**C**-OH); δ_P: 28.9 ppm. MS: m/z = 260 (M^+, 23%).

Pyrolysis of Adduct 15

Compound **15a** (0.3 g) was heated in a cold finger sublimator at 250°C (bath temperature) under reduced pressure (5 mm/Hg) for 30 min. The compound that sublimed was collected (58 mg, ~63%), recrystallized from dilute ethanol and proved to be 1,3-dimethyl-2-thiouracil (**2a**) (mp., mixed mps and comparative IR and MS spectra).[14]

Dimethyl phosphite was detected in the receiver by the development of a violet color on addition of 3,5-dinitrobenzoic acid in the presence of alkali.[28]

*Reaction of 1,3-dimethyl-2-thiouracil (***2a***) with* 5

A mixture of **2a** (0.7 g, 0.005 mol) and TAP **5a** or **5b** (4 ml) was heated at 100 °C for 12 h. After evaporation of the volatile materials *in vacuo*, the residual material was washed twice with cyclohexane and then recrystallized from chloroform to give in each reaction the dithione **22** as yellow crystals, mp. 186–188 °C (0.4 g, 62%). Anal. Calcd. for $C_{12}H_{16}N_4O_2S_2$ (312.41): C, 46.14; H, 5.16; N,

17.93; S, 20.52. Found: C, 45.73; H, 5.02; N, 17.69; S, 20.44%. IR (KBr) υ cm^{-1}: 1685 (C=O), 1627 (C=C). ^1H NMR ($CDCl_3$), δ ppm: 3.31 (12H, N-C**H**$_3$, s), 5.92, 7.62 (4H, C**H**=C**H**, 2d, J_{HH} = 4 Hz). MS: m/z = 312 (M^+, 50%), 248 (M^+-64 (2S), 100%). The cyclohexanes solution and the mother liquors were evaporated *in vacuo (with 5a)* to dryness, the residue, so obtained was triturated with acetone (5 ml) to give **15a** (<5%) (mp, mixed mp and TLC).

Reaction of 5-nitrouracil (3) *with TAP* (5a,b)

A mixture of compound **3** (1.5 g, 0.009 mol) and TMP (**5**a) or TEP (**5**b) (6 ml) was heated in the absence of solvent for 15 h. After evaporation of the volatile materials under reduced pressure, the residue was subjected to silica gel column chromatography by using the eluents stated below.

(In case of the first reaction with 5a)

Elution with pure chloroform yielded pyrimidine **27**a as yellow needles (0.8 g, 53.6%), mp. 293–295 °C (ethanol). Anal. Calcd. for $C_{12}H_{14}N_6O_4$ (306.28): C, 47.06; H, 4.61; N, 27.44. Found: C, 46.81; H, 4.37; N, 27.18%. IR (KBr) υ cm^{-1}: 3452 (NH), 1687 (C=O). ^1H NMR, δ ppm: 3.35 (12H, N-C**H**$_3$, s), 10.2 ppm (2H, N**H**, br). Ms: m/z = 306 (M^+, 16%).

Elution with pure ethanol eluted a colorless substance (1 mg, 15.7%), shown to be 1,3-dimethyl-5-nitrouracil (**4**a), mp. 153–155 °C (absolute ethanol) (mp., mixed mps and comparative IR and MS spectra).[29]

Under similar conditions, compound **27**a (72.3%) was also prepared by heating **4**a with trimethyl phosphite (**5**a) for 10 h.

(In case of the Second Reaction with 5b).

Fraction up to 1:1 v/v (cyclohexane-acetone) afforded yellow substance (0.5 g, 28.3%), mp. 193–195 °C (ethyl alcohol), proved to be 3-ethyl-5-nitrouracil (mp., mixed mps. and comparative IR and MS spectra).[30]

Fraction up to 4:6 v/v (cyclohexane-acetone) gave compound **27**b as yellow needles (1 g, 58.2%), mp. 282–284 °C (ethanol). Anal. Calcd. for $C_{16}H_{22}N_6O_4$ (362.39): C, 53.03; H, 6.12; N, 17.66. Found: C, 53.27; H, 5.92; N, 17.46%. IR (KBr) υ cm^{-1}: 3428 (NH), 1690 (C=O). ^1H NMR (DMSO): δ ppm, 1.24 (12H, $CH_2C\mathbf{H}_3$, t, J_{HH} = 3.91 Hz), 3.95 (8H, -C**H**$_2$-q), 9.32 (2H, N**H**, br). MS: m/z = 362 (M^+, 11%).

Reaction of 1 *and* 3 *with Dialkyl Phosphonates* (6a,b)

A mixture of 2-thiouracil (1) (1.3 g, 0.01 mol), dimethyl phosphonate (**6**a) and/or diethyl phosphonate (**6**b) (5 ml) and p-toluenesulfonic acid (p-TsOH) (30

mg) was heated in absence of solvent at 100 °C for 22 h. After evaporation of the volatile materials *in vacuo*, the residual substance was washed with H_2O then extracted with $CHCl_3$. After evaporation of $CHCl_3$, the residual substance was crystallized from the proper solvent and proved to be the monophosphonate **15**a or **15**b (~62%) (mp., mixed mp, and comparative IR and MS spectra).

Under similar conditions, the phosphonates **28**a,b were obtained by the reaction of 5-nitrouracil (**3**) with dimethyl or diethyl phosphonates (**6**a,b), respectively.

Dimethyl (1,3-dimethyl-5-nitrouracil-2-yl) phosphonate (**28**a) was obtained as colorless crystals (1.6 gm, 58.2%), mp. 113–115 °C (benzene). Anal. Calcd. for $C_8H_{12}N_3O_7P$ (293.18): C, 32.77; H, 4.13; N, 14.33; P, 10.57. Found: 32.54; H, 4.01; N, 14.08; P, 10.42%. IR (KBr) υ cm^{-1}: 1734, 1691 (C=O), 1501, 1342 ($-NO_2$), 1275 (P=O), 1030 (P-O-C). ^1H NMR, δ ppm: 3.02 (3H, N_1-C**H**$_3$, d, $^4J_{HP}$ = 3.5 Hz), 3.15 (3H, N_3-C**H**$_3$, s), 4.72, 4.75 (6H, P-O-C**H**$_3$, 2d, $^3J_{HP}$ = 10.5 Hz). δ_P = 24.8 ppm. MS: m/z = 293 (M^+, 18%).

Diethyl (1,3-diethyl-5-nitrouracil-2-yl) phosphonate (**28**b) was obtained as colorless crystals (2.1 g, 62.7%), mp. 185–187 °C (cyclohexane). Anal. Calcd. for $C_{12}H_{20}N_3O_7P$ (349.29): C, 41.26; H, 5.77; N, 12.03; P, 8.87. Found: C, 41.1; H, 5.53; N, 11.73; P, 8.52%. IR (KBr) υ cm^{-1}: 1710, 1695 (C=O), 1515, 1356 (NO_2), 1268 (P=O), 1078 (P-O-C). ^1H NMR, δ ppm, 1.2, 1.44 (12H, -CH_2-C**H**$_3$, 2m), 3.5–4.1 (8H, -C**H**$_2$-CH_3, m). δ_P = 25.3 ppm. MS: m/z = 349 (M^+, 44%).

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Endnotes

a. Yields of **15**a and **15**b was based on the starting material
b. ^{13}CNMR for compound **15**b is complex because of the overlap between the different types of alkyl groups.