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A Facile Synthesis of Pyrrolo-[3,2-*d*]pyrimidines from 6-Azidouracils and Ylide Phosphoranes

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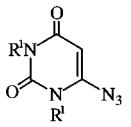
ABSTRACT: *A series of the title compounds, 9-deazaxanthines, was regioselectively prepared in reasonable yields as major products from the reactions of 6-azidouracils* **1a,b** *with stabilized ester-***2a,b** *or keto-***2c** *ylide phosphoranes and a moderated phosphorus ylide* **3**, *instead of the expected triazoles. Side products were also observed wherein pyrimido[5,4-g]pteridine-2,4,5,7-tetrone (***15***) and other fused ring systems or acyclic-substituted uracil derivatives were isolated. A comparative study on the reactivity of* **1a** *in analogy to* **1b** *toward phosphoranes is also described.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:357–365, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10048

INTRODUCTION

Uracils have presented a class of compounds that continually attracts organic chemists, medicinal chemists, and photobiologists [1–3]. Several uracil derivatives have been developed as drugs. Methylthiouracil and propylthiouracil are thyroid inhibitors; Bucolome is an antiinflammatory; and Uramustine (Uracil Mustard), Fluorouracil, and its masked compounds are anticancer agents. Uracil moieties were also detected in the antibiotic Tuicamycin [4a]. In addition, many mono- and bicyclic uracils are used to protect plants, mostly as herbicides [4b]. In a preceding communication, therefore, we described the synthesis of a series of phosphono-substituted uracils and some fused pyrimidines [5] as antimicrobial compounds.



1a, R^1 = H
1b, R^1 = Me

$Ph_3P{=}CHCOR$

2a, R = OMe
2b, R = OEt
2c, R = Ph

$Ph_3P{=}CH{-}CH{=}CH_2$

3

In the course of investigations of the chemical reactivity of alkylidenephosphoranes toward carbon–nitrogen systems [6], we now report the synthesis of the title compounds (also known as 9-deazaxanthines [7]) by reaction of stabilized ylides **2a–c** and moderated phosphorus ylide **3** with 6-azidouracil (**1a**) and 6-azido-1,3-dimethyluracil (**1b**). Some transformations of the products obtained are also reported. These heterocyclic-fused uracils might be useful for pharmaceutical purposes.

Because of its strongly polar groups, uracil itself shows only a weak solubility in organic solvents, and it is almost insoluble in alcohol. It is soluble in hot water and in aqueous alkali or ammonia, forming ionized species derived from **A** ⇌ **B**. Thus, uracil derivatives are, with a few exceptions, considered not suited for chemical reactions. For this reason, many research groups have chosen the 1,3-dimethyl

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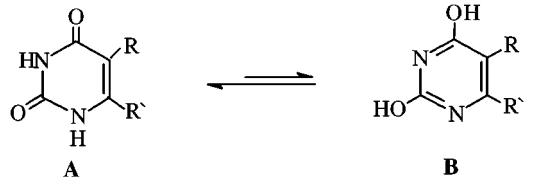
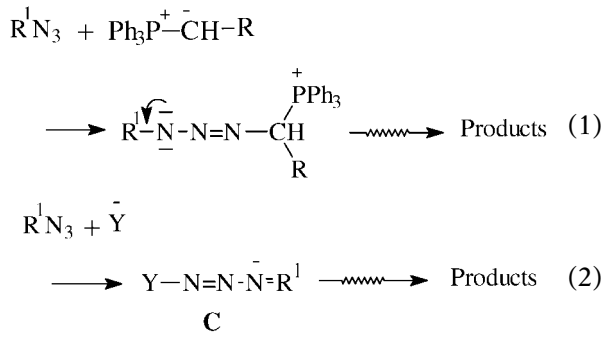
derivative as a versatile model compound. Therefore, a comparative chemical study of the behavior of **1a** in analogy with **1b** toward ylides **2** and **3** is herein undertaken.



A 2,4-(1 *H*,3*H*)Pyrimidinedione ⇌ **B** 2,4-Dihydroxypyrimidine

The reaction of phosphorus ylides with **1** might be expected to follow Eq. (1), analogous to the reactions of phosphines [8], alkyl phosphites [9], and carbanions [10] with 6-azidouracils. In these three cases, nucleophilic attack occurs on the azide terminus to give initially a triazo intermediate **C**, which may be either stable or else it decomposes to other products (Eq. (2)).



$$R^1N_3 + Ph_3P^{+}-\bar{C}H-R \longrightarrow R^1\bar{N}-N=N-CH(PPh_3^{+})(R) \rightsquigarrow \text{Products} \quad (1)$$

$$R^1N_3 + \bar{Y} \longrightarrow Y-N=N-\bar{N}-R^1 \rightsquigarrow \text{Products} \quad (2)$$

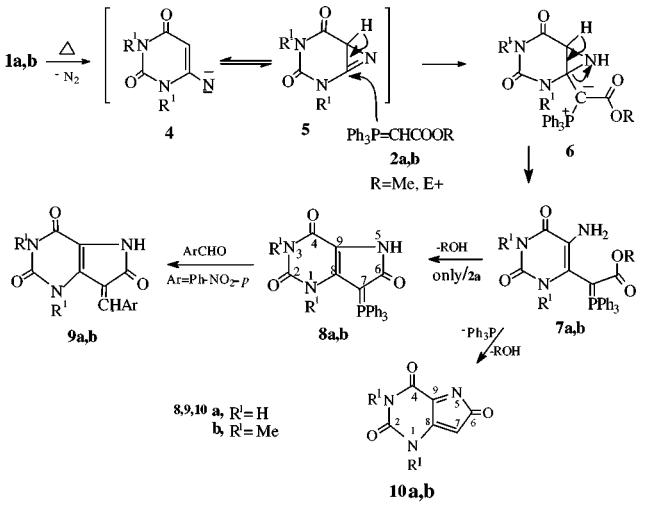
C

In reality, the reaction of alkylidenephosphoranes with **1** is not as straightforward as implied in Eq. (1). In fact, different routes leading to unexpected products have been observed.

RESULTS AND DISCUSSION

Reactions of **1a,b** *with Alkoxycarbonylmethylenetriphenylphosphorane* **2a,b**

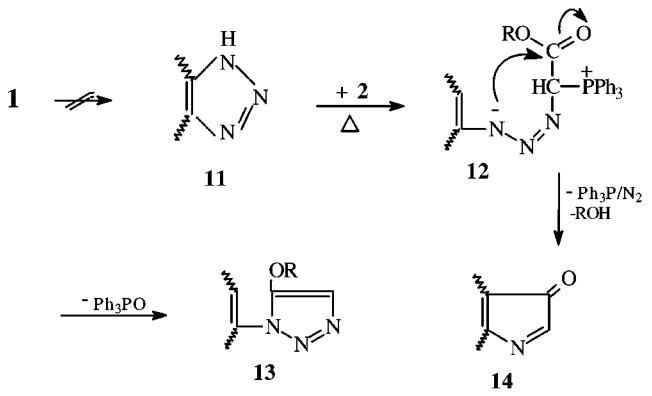
The reaction procedure for the preparation of the title compounds, pyrrolo[3,2-*d*]pyrimidines, and the course of the reactions are depicted in Schemes 1–6. The required starting materials 6-azidouracil (**1a**) and 6-azido-1,3-dimethyluracil (**1b**) were prepared according to the literature in ~75% yield by treating the parent chloride with sodium azide in ethanol [11]. An ethyl acetate solution of the azide **1a** and the ester ylide **2a** (1 mol equiv.) was heated under reflux for 10 h. Separation of the product mixture by column chromatography yielded (7-triphenylphosphoranylidene)pyrimido[5,4-*d*]-pyrrol-6-(5*H*)-one (**8a**) in 48% yield together with



SCHEME 1

pyrimido[5,4-*d*]pyrrol-6-one (**10a**) in 24% yield (Scheme 1). Triphenylphosphine oxide was not isolated or identified (TLC) in the reaction mixture. The recorded spectral data for pyrrole derivatives **8a** and **10a** were in agreement with the suggested structures (cf. Experimental section). Treatment of compound **8a** with aromatic aldehydes (e.g., *p*-nitrobenzaldehyde) in refluxing toluene for 48 h afforded 7-(4-nitrobenzylidene)-6-oxo-2,4 (1*H*,3*H*,5*H*)-pyrrolo[3,2-*d*]pyrimidinedione (**9a**) in 20% yield. When the same reaction was carried out in refluxing ethyl acetate for 18 h, compound **9a** (one isomer, Z-form) was again obtained, but in 72% yield. For similar reactions, pyrrolopyrimidines have also been reported in the literature [12]. Notwithstanding, more evidence is necessary for the configurational assignment of the product **9a.** The Z-configuration seems more favorable for the compound in question because of reduced steric hindrance.

A plausible mechanism for the formation of pyrrolidene phosphorane **8a** is presented in Scheme 1. Upon heating, denitrogenation occurs to form an intermediate nitrene **4**, which cyclizes to give a bicyclic azirine **5**, and is then intercepted by the addition reaction as discussed previously [13,14]. The addition of **2a** to **5** affords an aziridine intermediate **6**, which is followed by ring cleavage and recyclization to give the product **8a** via elimination of an alcoholic moiety (ROH). On the other hand, pyrrolone **10a** might arise from the intermediate **7a** via elimination of triphenylphosphine and an alcoholic moiety. Another possibility involves usual nucleophilic attack by **2** at the azide terminus to give an intermediate **12** (via **11**), followed by intramolecular cyclization accompanied with the loss of ROH, nitrogen,

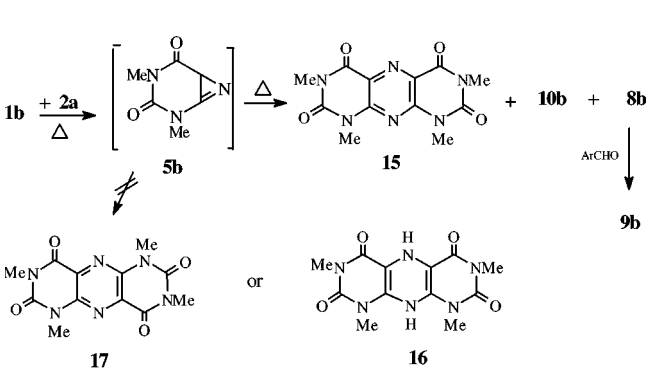


SCHEME 2

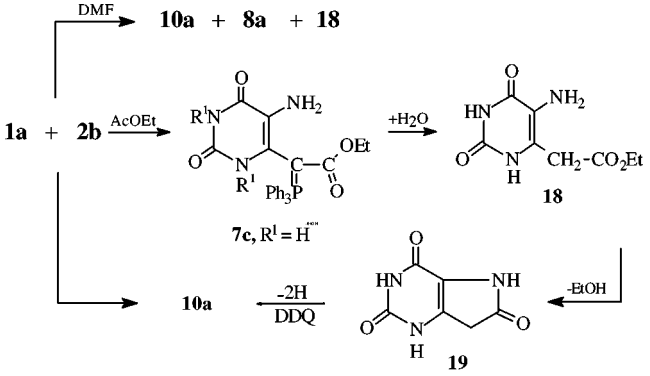
and triphenylphosphine, which also leads to the formation of the constitution-isomer **14** (Scheme 2). Nevertheless, formation of **14** via the intermediate **12**, according to the literature [15–17], is quite unfavorable; thus, it would rather lead to the formation of **13** and/or to the corresponding iminophosphorane. The structure **10a** has been, however, assigned to the product in question on the basis of IR and PMR spectral data in preference to **14**. For example, the data recorded for the methine proton (C-7-**H**) at $\delta = 6.15$ can readily eliminate from further consideration the compound **14** (C-acylaldimine) which would require a singlet between $\delta = 7.5$ and 8.5 ppm [N=C**H**–C(O)]. An attempt to convert **8** to **10** via dephosphorylation by heating in boiling ethyl acetate or pyrolysis was unsuccessful. However, identification of the structure **10** was established by an alternate synthesis of **10a** from the parent 5-aminouracil (see Scheme 4 and Eq. (3)).

When 6-azido-1,3-dimethyluracil (**1b**) was treated with an equimolar amount of **2a** under the same experimental conditions, products **8b** (28%), **10b** (13%), and the known [14] 1,3,6,8-tetramethylpyrimido[5,4-*g*]pteridine-2,4,5,7-tetrone (**15**) (17%) were obtained (Scheme 3). The structure **15** was easily established from its spectral data, reported by Yoneda et al. [14b]. The recorded mass spectrum, the analytical data, and the infrared spectrum of the yellow product **15**, m.p. >300°C, are also consistent with this assignment and exclude the expected structure **16** [18]. Furthermore, pteridine **15** has often been obtained as a by-product by the reaction of **1b** with a nucleophile [14a]. Nevertheless, the photochemical reaction of **1b** in organic solvents leads to 1,3,5,7-tetramethylpyrimido[4,5-*g*] pteridine-2,4,6,8-tetrone (**17**) [19]. Repetition of the reaction between **1b** and **2a** in dimethylformamide (DMF) afforded again the cyclic ylide **8b** as a major product (32%) along with compounds **10b** (15%) and **15** (22%). When the cyclic ylide **8b** was likewise allowed to react with an aromatic aldehyde, the normal Wittig reaction took place and yielded the olefin **9b** in 69% yield.

Treatment of the azide **1a** with an equimolar amount of ethoxycarbonymethylenetriphenylphosphorane (**2b**) in refluxing ethyl acetate for 10 h afforded ethyl 5-amino-2,4-(1*H*,3*H*)-pyrimidinedione-6-car-boxylate (**18**) (36%) and compound **10a** (26%) (Scheme 4). Compound **8a** was not isolated from this reaction mixture. The structure of compound **18** was confirmed by its analytical and spectral data. When the reaction between **1a** and **2b** was repeated in refluxing DMF, besides **10a** (25%), compounds **18** (25%) and **8a** (16%) were obtained. We consider that compound **18** arose through the previously suggested intermediate **7c**, which could be treated with water to give the pyrimidine **18** and triphenylphosphine oxide. The isolation of the cyclic product **8a** together with **18** from the reaction in DMF can be attributed to the higher temperature applied. When compound **18** was heated for 30 h in boiling toluene (or DMF), **18** was recovered unchanged. The pyrimidine **18**, however, when heated in a mixture of acetic anhydride and pyridine, underwent cyclization, furnishing the pyrrole **19**.

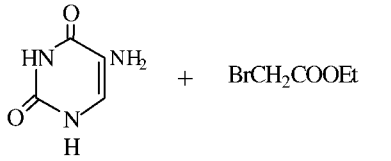


SCHEME 3



SCHEME 4

Treatment of **19** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided a second synthesis of **10a**, which was found to be identical with the product described above. Furthermore, compounds **18, 19**, and **10a** were independently synthesized and characterized (Eq. (3)). Thus, the ester **18**, prepared by treating 5-aminouracil with ethyl bromoacetate, was cyclized to **19** by refluxing in a mixture of acetic anhydride and pyridine. Conversion of **19** to **10a** could be accomplished by dehydrogenation with DDQ in chloroform solution.



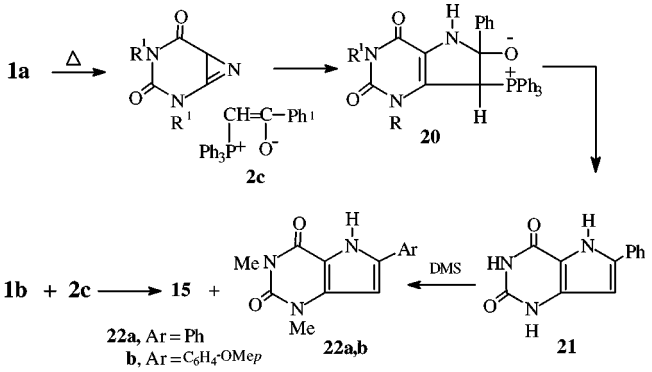
18 → **19** → **10a** (3)

6-Azido-1,3-dimethyluracil (**1b**), on the other hand, reacted with **2b** in either ethyl acetate or DMF (better yields in DMF) to give compounds **8b** (33%) and **10b** (19%) along with the pteridine **15** (13%) (Eq. (4)).

$$\mathbf{1b} + \mathbf{2b} \xrightarrow{\text{DMF}} \mathbf{8b} + \mathbf{10b} + \mathbf{15} \qquad (4)$$

Reaction of 6-Azidouracils **1a,b** *with Keto Ylide* **2c**

Next, the reactions of azides **1a,b** with benzoylmethylenetriphenylphosphorane (**2c**) were studied (Scheme 5). A DMF suspension of the azide **1a** and an equimolar amount of ylide **2c** was heated under reflux for 12 h and furnished 6-phenylpyrrolo[3,2-*d*]-pyrimidine (**21**) (63%) (along with other unidentified products of high melting points) according to the mechanism proposed in Scheme 5. Triphenylphosphine oxide was also isolated and identified. In order to provide additional support to the mechanism, pyrrole **21** was alkylated by the usual method to give



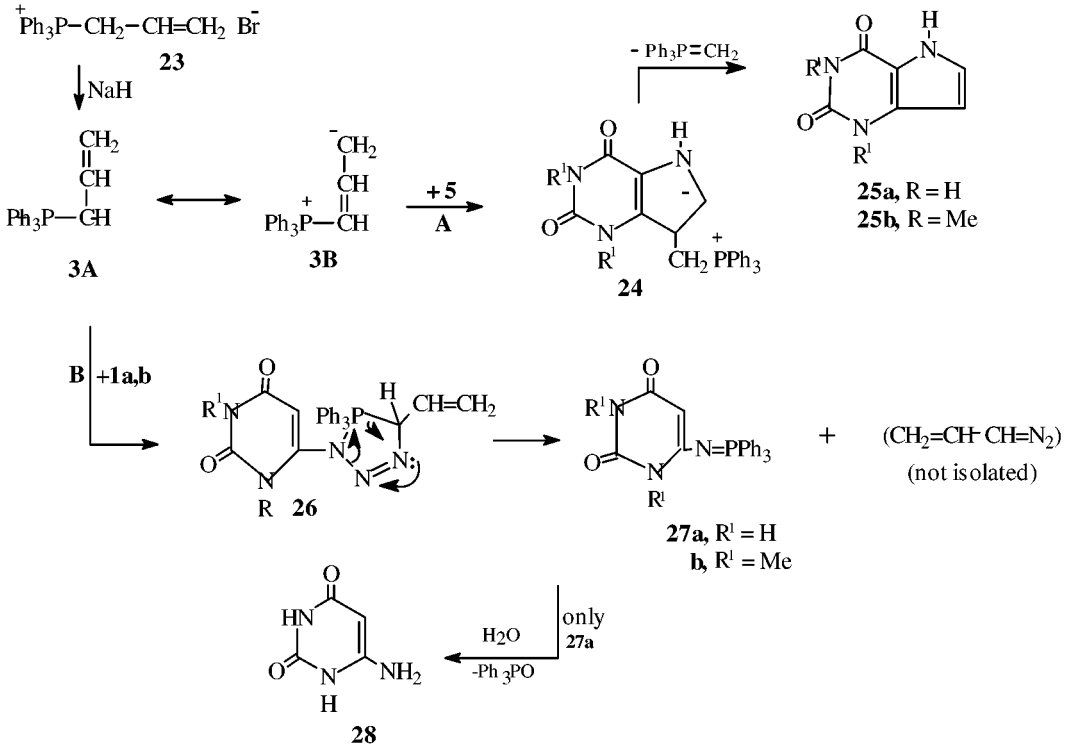
SCHEME 5

the known pyrrole **22a** in 55% yield, m.p. >300°C, previously reported by Senda et al. [20a]. Furthermore, compound **22a** (37%) and the pteridine **15** (18%) were obtained by treatment of **1b** with ylide **2c** in a way analogous to the one described for **1a** (Scheme 5).

It is worth mentionning here that the methods previously described for the preparation of pyrrolo-fused pyrimidines are lengthy and indirect [1,12,20,21]. For example, compound **22b** was synthesized by the condensation of 1,3,6-trimethyl-5-nitrouracil with benzaldehyde in ethanol. The 6-styryluracil produced was cyclized to **22b** on reduction or by treatment with triethyl phosphite, followed by irradiation in benzene [20b]. In the present context, compounds **21** and **22a** could be available by a one-step synthesis from the reaction of the proper 6-azidouracil with the keto ylide **2c**.

Reaction of 6-Azidouracils **1a,b** *with Allyl Phosphorane* **3**

Treatment of **1a** with allyltriphenylphosphorane (**3**), prepared in situ from its bromide salt **23**, in the presence of lithium hydride in ethyl methyl ketone yielded 6-aminouracil (**28**) [22] (26%) along with a white substance (43%), m.p. >300°C, and typical in all aspects with the known [23] 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[3,2-*d*]pyrimidine (**25a**). In a systemic study, compound **1b** was treated with the phosphonium bromide **23** under phase-transfer catalysis conditions, as described for **1a**, and afforded **25b** [7] (52%) and 1,3-dimethyl-2,4-dioxo-6-[(triphenylphosphoranylidene)amino]-1,2,3,4-tetrahydropyrimidine (**27b**) [24] (14%). A mechanism for the formation of the pyrrolo-fused pyrimidine **25** can be rationalized as occurring through the attack of the ylide **3B** on the initially formed azirine **5**, to generate the intermediate **24** (Scheme 6, A). Extrusion of methylidenephosphorane afforded compounds **25**. The reaction at the central carbon of the allyl group in **3** and further elimination of the phosphorane moiety is a documented process [25]. Furthermore, the ready elimination of the phosphonium species from **24** in the second step occurs through a carbanion mechanism, driven by the resulting gain in aromaticity. Concurrent with formation of the intermediate **24**, the triazole intermediate **26** is also produced. Collapse of **26** led directly to the phosphinimines **27a,b**. Further hydrolysis of **27a** gave **28**. The absence of compound **15** and the appearance of the intermediate **26** were, however, attributed to the short time of heating in the latter reaction (**1b** + **3**).



SCHEME 6

Turning now to the scope of the above three reactions of **1a** and **1b** with ester-**2a,b**, keto-**2c**, and moderated allyl-**3** ylides, some concluding remarks can be made: (1) the results clearly showed a marked resemblance between the substrates **1a** and **1b** in their chemical behavior toward triphenylmethylenephosphoranes; (2) the azirine intermediate **5**, generated from the parent azide via denitrogenation, is a key intermediate for subsequent transformations; (3) the construction of different hetero products depends upon the electronic characteristic of the ylide used and the experimental conditions.

Finally, the present work describes an efficient and simple approach to the synthesis of a variety of 9-deazaxanthine derivatives (cf. compounds **8a,b, 9a,b, 10a,b, 21, 22a**, and **25a,b**) in reasonable yields. This general method consists of suitable applications of the appropriate ylide phosphorane with 6-azidopyrimidines. Data on the pharmaceutical potency of the new compounds **8a,b, 10a,b, 9a,b**, and **18** will be published elsewhere.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer model 297 (Grating) using KBr discs. The ^{1}H and ^{13}C NMR spectra were run on a Varian Gemini 200 (200 MHz) instrument, using TMS as an internal reference. The ^{31}P NMR spectra were recorded relative to external H_3PO_4 (85%) with a Varian CFT-80 instrument. The mass spectra were performed at 70 eV on an MS-50 Kratos (A.E.I.) spectrometer provided with a data system. The appropriate precautions in handling moisture-sensitive compounds were observed.

*Reaction of 6-Azido-2,4(1H,3H)-pyrimidinedione (**1a**) with Methoxycarbonylmethylene(triphenyl)phosphorane (**2a**): Preparation of Compounds **8a** and **10a***

(A) A stirred suspension of 6-azidouracil (**1a**) (0.8 g, 5.2 mmol) and the ylide **2a** (1.83 g, 5.5 mmol) in dry ethyl acetate (20 ml) was boiled under reflux for 10 h. After removal of the solvent the residue was chromatographed on silica gel. Elution with dichloromethane–ethyl acetate (CH_2Cl_2–AcOEt; 3:7 → 0:10 v/v) and further with pure methyl alcohol afforded two fractions. The first fraction gave colorless crystals of 2,4-(1*H*,3*H*,6*H*)-6-oxo-pyrrolo[3,2-*d*]pyrimidinedione (**10a**) (210 mg, 24%), m.p. 315–317°C (from AcOEt) (Found: C, 43.73; H, 1.77; N, 25.31. $C_6H_3N_3O_3$ (165.11) requires: C, 43.64; H, 1.83; N, 25.45%); ν_{max}(KBr)/cm^{-1} 3330$_W$ (NH), 1735 (C-6-(O)], 1685, 1635 [C-4-(O), C-2-(O)], 1622 (C=CH); δ_H (d_6-DMSO) 6.15 (s, 1H, C-7-**H**), 9.95, 11.43 (2 × s,

2 × 1H, N-3-**H**, N-1-**H**, deuterium exchangeable); δ_C 99.2 (**C**-9), 133.6 (**C-7-**H), 149.5 (**C**-8), 152.2, 164.8 (**C**-2-(O), **C**-4-(O)], 171.3 [**C**-6-(O)]; *m/z* (%) 165 (100) [M^+], 122 (66) [$M^+ - 43$, HNCO].

The second fraction gave colorless crystals of 6-oxo-7-(triphenylphosphoranylidene)-2,4(1*H*, 3*H*, 5*H*)pyrrolo[3,2-*d*]pyrimidinedione (**8a**) (1.1 g, 48%), m.p. 328–330°C (from ethyl alcohol) (Found: C, 67.56; H, 4.19; N, 9.71; P, 7.22. $C_{24}H_{18}N_3O_3P$ (427.41) requires: C, 67.44; H, 4.24; N, 9.83; P, 7.25%); ν_{max}(KBr)/cm^{-1} 3230, 3342 (NH), 1687, 1645 [C-4-(O), C-2-(O)], 1610 [C-5-(O)], 1483 (=PPh_3), 980 (P-C, Ph-**H**); δ_P (d_6-DMSO) 14.88; δ_H 7.44–7.86 (m, 15H, Ar-**H**), [8.54 (s, 1H, N-5-**H**), 9.95 (s, 1H, N-3-**H**), 11.33 (d, J_{HP} = 9.5 Hz, N-1-**H**, deuterium exchangeable); δ_C 89.3 (d, $^2J_{CP}$ = 103.5 Hz, **C**=P), 110.8 (**C**-9), 141.2 (d, J_{CP} = 15.7 Hz, **C**-8), 152.5, 163.4 [2d, **C**-2-(O), **C**-5-(O)], 155.3 [d, J_{CP} = 18.5 Hz, **C**-6-(O)]; *m/z* (%) 427 (11) [M^+], 384 (32) [$M^+ - 43$, HNCO], 341 (20) [($M^+ - 43$) − 43, HNCO], 262 (9) (Ph_3P), 165 (100) [$M^+ - 262$, Ph_3P].

(B) A sample of **8a** (0.1 g) was refluxed in DMF (or toluene) (5 ml) for 20 h. After evaporation of the solvent in vacuo, the yellow solid that remained was collected (>90%) with a small amount of chloroform and shown to be identical with **8a** (TLC and comparative IR and mass spectra).

(C) Pyrolysis of 0.1 g of **8a** at 250°C (0.01 mm) for 2 h gave a dark lavender mass which afforded unidentified products on chromatography.

*Reaction of 6-Azido-1,3-dimethyl-2,4-(1H,3H)-pyrimidinedione (***1b***) with* **2a***: Preparation of Compounds* **8b, 10b** *and* **15**

(A) A stirred solution of the azide **1b** (0.8 g, 4.42 mmol) and the ylide **2a** (1.56 g, 4.5 mmol) in dry ethyl acetate (20 ml) was heated at reflux for 8 h. After cooling to room temperature, the precipitated crystals were collected, recrystallized from DMF, and identified as 1,3,6,8-tetramethylpyrimido[5,4-*g*]pteridine-2,4,5,7-(1*H*,3*H*,6*H*,8*H*)-tetrone (**15**) (115 mg, 17%), m.p. >300°C (Lit. [14b], m.p. >300°C); *m/z* (%) 304 (66) [M^+].

The filtrate was separated by column chromatography on silica gel, CH_2Cl_2—AcOEt as eluent (3:7 → 0:10 v/v) afforded two fractions. The first fraction furnished colorless crystals of 1,3-dimethyl-2,4(1*H*,3*H*,6*H*)-6-oxo-pyrrolo[3,2-*d*]pyrimidinedione (**10b**) (110 mg, 13%), m.p. 253–255°C (from $CHCl_3$) (Found: C, 49.67; H, 3.52; N, 21.67. $C_8H_7N_3O_3$ (193.17) requires: C, 49.74; H, 3.65; N, 21.75%); ν_{max}(KBr)/cm^{-1} 1735 [C-6-(O)], 1674, 1624 [C-4-(O), C-2-(O)], 1618 (C=CH); δ_H (d_6-DMSO) 3.25 (br.s, 6H, 2 × N-C**H**$_3$), 5.88 (s, 1H, C=C**H**); δ_C 27.8 (2 × N-**C**H_3), 98.4 (**C**-9), 131.4 (**C-7-**H), 148.8 (**C**-8), 151.8, 163.4 [**C**-2-(O), **C**-4-(O)], 170.3 [**C**-6-(O)]; *m/z* (%) 193 (30) [M^+].

The second fraction yielded colorless crystals of 1,3-dimethyl-6-oxo-7(triphenylphosphoranylidene)-2,4(1*H*,3*H*,5*H*)pyrrolo[3,2-*d*]pyrimidinedione (**8b**) (563 mg, 28%), m.p. 308–310°C (from methyl alcohol) (Found: C, 68.71; H, 4.81; N, 9.14; P, 6.83. $C_{26}H_{22}N_3O_3P$ (455.45) requires: C, 68.56; H, 4.87; N, 9.23; P, 6.8%); ν_{max}(KBr)/cm^{-1} 3245, 3340 (NH), 1680, 1635 [C-4-(O), C-2-(O)], 1620 [C-6-(O)], 1485 (=PPh_3), 980 (P-C, Ph-**H**); δ_P (d_6-DMSO) 15.66 ppm; δ_H 2.40 (d, 3H, N-1-C**H**$_3$), 3.12 (S, 3H, N-3-C**H**$_3$), 7.23–7.85 (m, 15H, Ph-**H**), 8.83 (s, 1H, N-5-**H**, deuterium exchangeable); δ_C 29.2, 29.4 (2 × N-**C**H_3), 87.4 (d, $^2J_{CP}$ = 107.4 Hz, **C**=P), 105.3 (**C**-9), 143.6 (d, J_{CP} = 15.5 Hz,**C**-8), 151.8, 162.6 [2d, **C**-2-(O), **C**-4-(O)], 154.4 [d, J_{CP} = 18.2 Hz, **C**-6-(O)]; *m/z* (%) 455 (15) [M^+], 193 (100) [$M^+ - 262$, Ph_3P].

(B) The reaction between equimolar amounts of compounds **1b** and **2a** in dry DMF under the conditions described above, afforded compounds **8b** (670 mg, 32%), **10b** (128 mg, 15%), and **15** (147 mg, 22%), which were identical with the products obtained previously.

Wittig Reaction of Ylides **8a,b** *with p-Nitrobenzaldehyde: Preparation of Compounds* **9a,b**

(A) To a stirred suspension of ylide **8a** (0.3 g, 0.7 mmol) in toluene (10 ml) *p*-nitrobenzaldehyde (113 mg, 0.75 mmol) was added and the reaction mixture was heated under reflux for 48 h. After the evaporation of the solvent the residue was triturated with chloroform to give 7(4-nitrobenzylidene)-6-oxo-2,4(1*H*,3*H*,5*H*)pyrrolo[3,2-*d*]pyrimidinedione (**9a**) (42 mg, 20%), m.p. 316–318°C (from ethyl alcohol) (Found: C, 52.08; H, 2.62; N, 18.48. $C_{13}H_8N_4O_5$ (300.24) requires: C, 52.00; H, 2.68; N, 18.66%); ν_{max}(KBr)/cm^{-1} 3230, 3340_w (NH), 1695, 1640 [C-4-(O), C-2-(O)], 1615 [C-6-(O)], 1598 (C=CH); δ_H (d_6-DMSO) 7.24–7.44 (m, 4H, Ph-**H**), 7.82 (d, 1H, *J* = 4.2 Hz, =C**H**), 8.58 (s, 1H, N-5-**H**), 9.72 (d, diffused, 1H, N-1-**H**), 10.02 (s, 1H, N-3-**H**, deuterium exchangeable); *m/z* (%) 300 (33) [M^+].

When the same reaction (**8a** + *p*-nitrobenzaldehyde) was repeated in boiling ethyl acetate for 18 h (TLC), compound **9a** (150 mg, 72%) was obtained.

(B) A solution of the ylide **8b** (0.3 g, 0.66 mmol) and *p*-nitrobenzaldehyde (100 mg, 0.68 mmol) in ethyl acetate (10 ml) was heated under reflux for 14 h. After evaporation of the solvent the residue was triturated with dichloromethane to yield yellow leaflets of 1,3-dimethyl-7(4-nitrobenzylidene)-6-oxo-2,4(1*H*,3*H*,5*H*)pyrrolo[3,2-*d*]pyrimidinedione (**9b**)

(149 mg, 69%), m.p. 286–288°C (from ethyl alcohol) (Found: C, 54.94; H, 3.62; N, 16.90. $C_{15}H_{12}N_4O_5$ (328.29) requires: C, 54.88; H, 3.68; N, 17.07%); ν_{max}(KBr)/cm^{-1} 3225 (NH), 1680, 1635 [C-4-(O), C-2-(O)], 1612 [C-6-(O)], 1605 (C=CH); δ_H 2.54 (d, $J_{HH} = 3.5$ Hz, 3H, N-1-C**H**$_3$), 3.23 (s, 3H, N-3-C**H**$_3$), 7.43–7.84 (m, 4H, Ph-**H**), 7.85 (q, $J_{HH} = 3.5$ Hz, =C**H**), 8.74 (s, 1H, N-5-**H**, deuterium exchangeable); *m/z* (%) 328 (40) [M$^+$].

*Reaction of 6-Azidouracil (***1a***) with Ethoxycarbonylmethylene(triphenyl)phosphorane (***2b***): Preparation of Compounds* **8a, 10a** *and* **18**

(A) The reaction between the azide **1a** (0.8 g, 5.2 mmol) and the ylide **2b** (1.8 g, 5.25 mmol) in boiling ethyl acetate (20 ml) for 8 h was carried out and the reaction mixture was worked up according to the above described procedure for ylide **2a**. Ethyl 5-amino-2,4-dioxo(1*H*, 3*H*)pyrimidine-6-carboxylate (**18**) was eluted first (410 mg, 36%), m.p. 322–323°C (from dioxan) (Found: C, 45.18; H, 5.12; N, 19.58. $C_8H_{11}N_3O_4$ (213.2) requires: C, 45.07; H, 5.20; N, 19.71%); ν_{max}(KBr)/cm^{-1} 3325$_w$ (NH), 3410 (NH$_2$), 1727 [C(O), ester], 1690, 1642 [2 × C(O), amides]; δ_H (d_6-DMSO) 1.05 (t, $J_{HH} = 7.3$ Hz, 3H, CH$_2$—C**H**$_3$), 3.15 (s, 2H, C**H**$_2$), 3.85 (s, 2H, N**H**$_2$, deuterium exchangeable), 3.96 (q, $J_{HH} = 7.3$ Hz, C**H**$_2$—CH$_3$), 10.04, 11.52 (2 × s, 2 × 1H, N-3-**H**, N-1-**H**, deuterium exchangeable); δ_C 13.9 (CH$_2$**C**H$_3$), 48.6 [**C**H$_2$—C(O)], 61.6 (**C**H$_2$CH$_3$), 117.3 (**C**-6), 148.9 (**C**-5), 152.4 (**C**-4), 161.8 (**C**-2), 169.3 (**C**-8); *m/z* (%) 213 (100) [M$^+$].

The second fraction afforded compound **10a** (223 mg, 26%).

(B) The reaction between the azide **1a** (0.4 g, 2.6 mmol) and the ylide **2b** (0.9 g, 2.62 mmol) in boiling DMF (15 ml) for 8 h was carried out and the product mixture was worked up as above to give first compound **18** (142 mg, 25%). The next fraction afforded compound **10a** (107 mg, 25%). The third fraction gave ylide **8a** (178 mg, 16%).

Conversion of **18** *into* **19**

The pyrimidine **18** (0.1 g) in a mixture of acetic anhydride (1.0 ml) and pyridine (2 ml) was heated on a steam bath for 30 min. The reaction mixture was kept overnight and the solid that separated was filtered off, washed well with a small amount of water, and finally crystallized from ethanol to give compound **19** as white flakes (47 mg, 60%), m.p. 318–320°C (Found: C, 43.22; H, 2.94; N, 25.05. $C_6H_5N_3O_3$ (167.13) requires: C, 43.12; H, 3.01; N, 25.14%); ν_{max}(KBr)/cm^{-1} 3330$_w$ (NH), 1687, 1635, 1615 [3 × C(O)]; δ_H (d_6-DMSO) 4.72 (br.s, 2H, C**H**$_2$), 8.83 (s, 1H, N-5-**H**), 9.95 (s, 1H, N-3-**H**), 10.72 (dd, $J = 4.5$, 1.0 Hz, N-1-**H**, deuterium exchangeable); *m/z* (%) 167 (100) [M$^+$].

(B) A sample of compound **18** (0.1 g) was refluxed in DMF (or toluene) (5 ml) for 30 h. After evaporation of the solvent in vacuo, the residual yellow solid was taken up (>90%) with a small amount of chloroform and shown to be identical with **18** (TLC and comparative IR and mass spectra).

Conversion of **19** *into* **10a**

To a stirred solution of 0.14 g (0.4 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 50 ml of chloroform was added 0.05 g (0.3 mmol) of **19**, and the mixture was heated under reflux for 1 h, and then concentrated to dryness under reduced pressure. The residual solid was extracted with 5 ml of warm ethanol to remove the formed hydroquinone (TLC). Recrystallization of the residual solid from ethyl acetate gave 31 mg (63%) of **10a**, m.p. 315–317°C, identical with the material prepared as described above by using **2a**.

Preparation of Compounds **18, 19** *and* **10a**

The procedure reported by Ogura et al. [26] for the alkylation of 6-amino-1,3-dimethyluracil at the 5-position was modified as follows: A mixture of 2.5 g (0.02 mol) of 5-aminouracil (available from Aldrich) and 4.2 g (0.025 mol) of ethyl bromoacetate in 100 ml of acetonitrile was heated under reflux for 4 h. After removal of the solvent the residue was chromatographed on silica gel. Elution with CH_2Cl_2–AcOEt (3:7 → 0:10 v/v) gave colorless crystals of **18** (0.92 g, 22%), m.p. 323–325°C (from dioxan) and other unidentified products. Compound **18** was converted to **19** by heating in a mixture of acetic anhydride and pyridine. Dehydrogenation of **19** by DDQ afforded **10a**. The prepared compounds **18, 19**, and **10a** are identical in all aspects with the materials previously obtained.

*Reaction of 6-Azido-1,3-dimethyluracil (***1b***) with Ylide* **2b***: Preparation of Compounds* **8b, 10b** *and* **15**

To a stirred solution of the azide **1b** (0.8 g, 4.42 mmol) and the ylide **2b** (1.53 g, 4.42 mmol) in ethyl acetate (or DMF, best yields in DMF) (20 ml) was heated under reflux for 8 h. The hot product mixture was then filtered to give crystals of compound **15** (87 mg, 13%). The filtrate was evaporated to dryness. Chromatography with CH_2Cl_2–AcOEt (3:7 v/v)

as eluent afforded compound **10b** (160 mg, 19%) and then elution with pure ethyl acetate gave compound **8b** (0.69 g, 33%).

Reaction of **1a** *with Benzoylmethylenetriphenylphosphorane (***2c***): Preparation of Compound* **21**

A stirred suspension of the azide **1a** (0.8 g, 5.2 mmol) and the ylide **2c** (2.1 g, 5.5 mmol) in ethyl acetate (20 ml) was heated under reflux for 12 h and then evaporated to dryness. Chromatography on silica gel with pure ethanol afforded 6-phenyl-2,4(1*H*,3*H*,5*H*)-pyrrolo[3,2-*d*]pyrimidinedione (**21**) (744 mg, 63%), m.p. >300°C (from ethyl alcohol) (Found: C, 63.55; H; 3.87, N; 18.36. $C_{12}H_9N_3O_2$ (227.23) requires: C, 63.43; H, 3.99; N, 18.49%); ν_{max}(KBr)/cm^{-1} 3340$_W$ (NH), 1687, 1638, [C-4-(O), C-2-(O)]; δ_H (d_6-DMSO) 6.55 (s, 1H, C-7-**H**), 7.45-7.76 (m, 5H, Ph-**H**), 8.55 (s, 1H, N-5-**H**), 9.94, 11.32 (2 × s, 2 × 1H, N-3-**H**, N-1-**H**, deuterium exchangeable); *m/z* (%) 227 (100) [M$^+$].

*Preparation of 1,3-Dimethyl-6-phenyl-2,4-(1H,3H,5H)pyrrolo[3,2-d] pyrimidinedione(***22a***)*

To a stirred solution of **21** (0.2 g, 0.88 mmol) in NaOH (5 ml, aqueous, 40%), dimethyl sulfate (252 mg, 2 mmol) was added dropwise (~0.5 h) at room temperature. The reaction mixture was heated to boiling, cooled, then extracted thrice with 30 ml each of chloroform and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was triturated with CH_2Cl_2 to give compound **22a** (100 mg, 45%), m.p. >300°C (from DMF) (Lit. [20a], m.p. >300°C); *m/z* (%) 255 (100) [M$^+$].

Preparation of Compounds **22a** *and* **15**

A solution of **1b** (0.8 g, 4.42 mmol) and ylide **2c** (1.69 g, 4.45 mmol) in DMF (20 ml) was heated under reflux for 10 h. The hot product mixture was then filtered to give **15** (120 mg, 18%). After removal of the solvent from the filtrate the residue was chromatographed with CH_2Cl_2–AcOEt (2:8 v/v) as eluent to give **22a** (417 mg, 37%).

Reaction of 6-Azidouracils **1a,b** *with Allyltriphenylphosphorane* **3***: Preparation of Compounds* **25a,b, 27b**, *and* **28**

General Procedure. To a slurry of 95 mg of lithium hydride (LiH) dispersion (57% in mineral oil) in 10 ml of dry ethyl methyl ketone was added dropwise 2.1 g (5.5 mmol) of the phosphonium salt **23** in 10 ml of the same solvent. The reaction mixture was stirred at room temperature until all hydrogen evolution had ceased (~1 h), and the azide **1a** or **1b** (5.2 mmol) was introduced all at once. The reaction mixture was allowed to remain at room temperature for a further 2 h and then refluxed for 2 h. The product mixture was concentrated to 10 ml, diluted with 30 ml distilled H_2O, acidified with conc. HCl and then extracted with two 100 ml portions of ethyl acetate. The ethyl acetate extracts were combined, back washed with 100 ml of H_2O, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was chromatographed on silica gel with CH_2Cl_2–AcOEt (2:8 v/v) and further with methanol as eluents to give two fractions.

With **1a**. The first fraction afforded colorless crystals of 2,4-dioxo(1*H*,3*H*,5*H*)-pyrrolo[3,2-*d*]pyrimidine (**25a**) (280 mg, 36%), m.p. 311–312°C (from methanol, Lit. [23], m.p. >300°C); *m/z* (%) 151 (100) [M$^+$]. The second fraction afforded colorless crystals of 6-aminouracil (**28**) (153 mg, 26%), m.p. >330°C (from ethyl alcohol, Lit. [22], 312–315°C); *m/z*(%) 127 (100) [M$^+$].

With **1b**. The reaction afforded 9-deazaxanthine **25b** (52%), m.p. 212–214°C (from $CHCl_3$, Lit. [7], 210°C); *m/z* (%) 179 (100) [M$^+$], and 1,3-dimethyl-2,4-dioxo-6[(triphenylphosphoranylidene)-amino]-1,2,3,4-tetrahydropyrimidine (**27b**) [24] (14%).

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