# ON THE REACTIONS OF 6-PHOSPHORANYLIDENEAMINOURACILS AND RELATED 6-AMINOURACILS WITH 2,4,6-CYCLOOCTA-TRIENONE: REACTIONS OF THE INTERMEDIATES OF URACIL-ANNULATED 8-AZABICYCLO[5.3.1]UNDECATETRAENE RING SYSTEMS

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Abstract-The reaction of 1,3-dimethyl-6-phosphoranylideneaminouracil (**4**) with 2,4,6-cyclooctatrienone (**7**) in AcOH gives an intermediacy of uracil-annulated 8-azabicyclo[5.3.1]undeca-2,4,7,9-tetraene (**9**), which results in the formation of 9-acetoxy-5a,10-methano-2,4-dimethyl-2*H*-5,5a,6,8a,9,10-hexahydrocyclopent[*b*]-pyrimido[5,4-*f*]azepine-1,3(4*H*)-dione and 1,3,7- and 1,3,5-trimethylpyrido[2,3-*d*]pyrimidine-2(1*H*),4(3*H*)-diones (**12** and **13**) after several reaction sequences. A similar reaction using 6-amino-1,3-dimethyluracil (**5**) also afforded the same products probably *via* uracil-annulated 8-azabicyclo[5.3.1]undeca-2,4,6,9-tetraene (**14**). A similar intermediate is also postulated in the reaction of 3-methyl-6-methylaminouracil (**6**) with 2,4,6-cyclooctatrienone, and results in the formation of 9-acetoxy-5a,10-methano-2,4,5-trimethyl-2*H*-5,5a,6,8a,9,10-hexahydrocyclopent-[*b*]pyrimido[5,4-*f*]azepine-1,3(4*H*)-dione (**26**), 3,7,8- and 3,5,8-trimethylpyrido-[2,3-*d*]pyrimidine-2(3*H*),4(8*H*)-diones (**27** and **28**).

Fused pyrimidines, which are common sources for the development of new potential therapeutic agents, are well known.[1,2] Among these, 5-deazaflavins (5-deazaalloxazine and 5-deazaisoalloxazine) have been studied extensively in both enzymatic and model systems in the hope of providing mechanistic insight into flavin-catalyzed reactions.[3-5] We have been interested in exploiting the unique reactivity afforded by the vinyliminophosphoranes[6] and related compounds[7] in developing efficient strategy for the preparation of fused heterocycles. In most cases, a few easy reaction steps enable the synthesis of novel

1a: n = 0
 b: n = 1

2a: n = 0
 b: n = 1

3a: n = 0
 b: n = 1

Scheme 1.
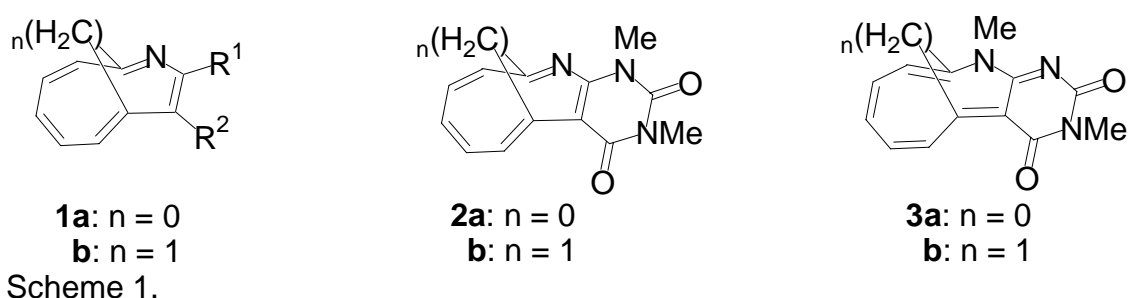
and highly interesting types of ring-annulated heterocycles, which are difficult to obtain by other synthetic procedures.   Since 1-azaazulene derivatives have attracted much attention in view of their pharmacological activities,[9] and simple 1-azaazulenes (**1a**) are accessible by the reaction of vinyliminophosphoranes[6] and related compounds,[8,9] we have previously reported methodology to synthesize 7,9-dialkylcyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(7*H*),10(9*H*)-dione (**2a**)[11] and 6,9-disubstituted cyclohepta[*b*]pyrimido[5,4-*d*]pyrrole-8(6*H*),10(9*H*)-diones (**3a**),[12] and a catalytic function of the latter compounds for the oxidation of alcohols as in the case of the 5-deazaflavins.   In this context, as well as to pursue our continuing interest in synthesizing novel 8-azabicyclo[5.3.1]undeca-1,3,5,7,9-pentaene (**1b**),[13] we have now investigated the reactions of 1,3-dimethyl-6-phosphoranylideneamino- and 6-amino-1,3-dimethyluracils (**4**) and (**5**) as well as 3-methyl-6-methylaminouracil (**6**) with 2,4,6-cyclooctatrienone (**7**) to synthesize uracil-annulated bridged annulenes (**2b**) and (**3b**), which are an isoelectronic π-system of **2a** and **3a**, respectively.   We report herein the results, which involve several interesting reactions of the intermediates, uracil-annulated 8-azabicyclo[5.3.1]undecatetraene skeletons, in detail.

The reaction of **4**[2,14] with **7**[15] in AcOH in the presence of a dehydrogenating agent (10% Pd/C) under reflux for 60 h afforded 9-acetoxy-5a,10-methano-2,4-dimethyl-2*H*-5,5a,6,8a,9,10-hexahydro-cyclopent[*b*]pyrimido[5,4-*f*]azepine-1,3(4*H*)-dione (**11**), 1,3,7-, and 1,3,5-trimethylpyrido[2,3-*d*]-pyrimidine-2(1*H*),4(3*H*)-diones (**12**) and (**13**) (Scheme 2 and Table 1, Entry 1).   The formation of **11**-**13** can be reasonably explained as follows.   The Michael addition of **4** to the β-carbon atom of **7** gives **8**, which undergoes the intramolecular aza-Wittig reaction eliminating Ph$_3$PO to give a constrained **9** as in the reaction of simple vinyliminophosphorane with **7**.[13]   Compound (**9**), which contains a double bond and a cyclohexadiene unit in an appropriate stereochemical situation,[16] is not dehydrogenated to give compound (**2b**) in the presence of 10% Pd/C, and undergoes the aza-Diels-Alder reaction to afford compound (**10**). Compound (**10**) then undergoes AcOH-assisted ring-opening reaction to yield the final product (**11**).   On the other hand, AcOH-catalyzed hydrogen migration of compound (**9**) affords two isomeric compounds (**14**) and (**15**), which undergo conrotatory ring opening and subsequent disrotatory ring closure to result in the formation of **17** and **20**, respectively.   A plausible Diels-Alder reaction of compounds (**17**) and (**20**) with **7** and the subsequent retro-Diels-Alder reaction eliminating **18** and hydrogen migration result in the formation of **12** and **13**, respectively.   Attempted isolations of compound (**18**) or benzocyclooctadienone, which may originate from the sequential 1,5-hydrogen migration of **18**, were unsuccessful.   Furthermore, an attempted reaction of **4** with **7** in refluxing xylene (Table 1, Entry 2) did not afford any product, and only decomposition reactions of the starting materials were observed.   Thus, the present reaction is apparently assisted by the AcOH catalyst.

Compound (**12**) and (**13**)[17,18] are known and identified on the basis of the comparison of the physical data with those reported in the literature.   The structure of compound (**11**) was confirmed from an inspection of the spectroscopic data including ^{1}H NMR and IR spectral data, HRMS data, and finally X-Ray crystal structure analysis (Figure 1).   The X-Ray crystal analysis revealed unequivocally that the AcO- group is introduced in the *exo*-position as expected from the mechanistic aspect and ^{1}H NMR spectral data ($J_{8a,9}$ = 3.4 Hz).
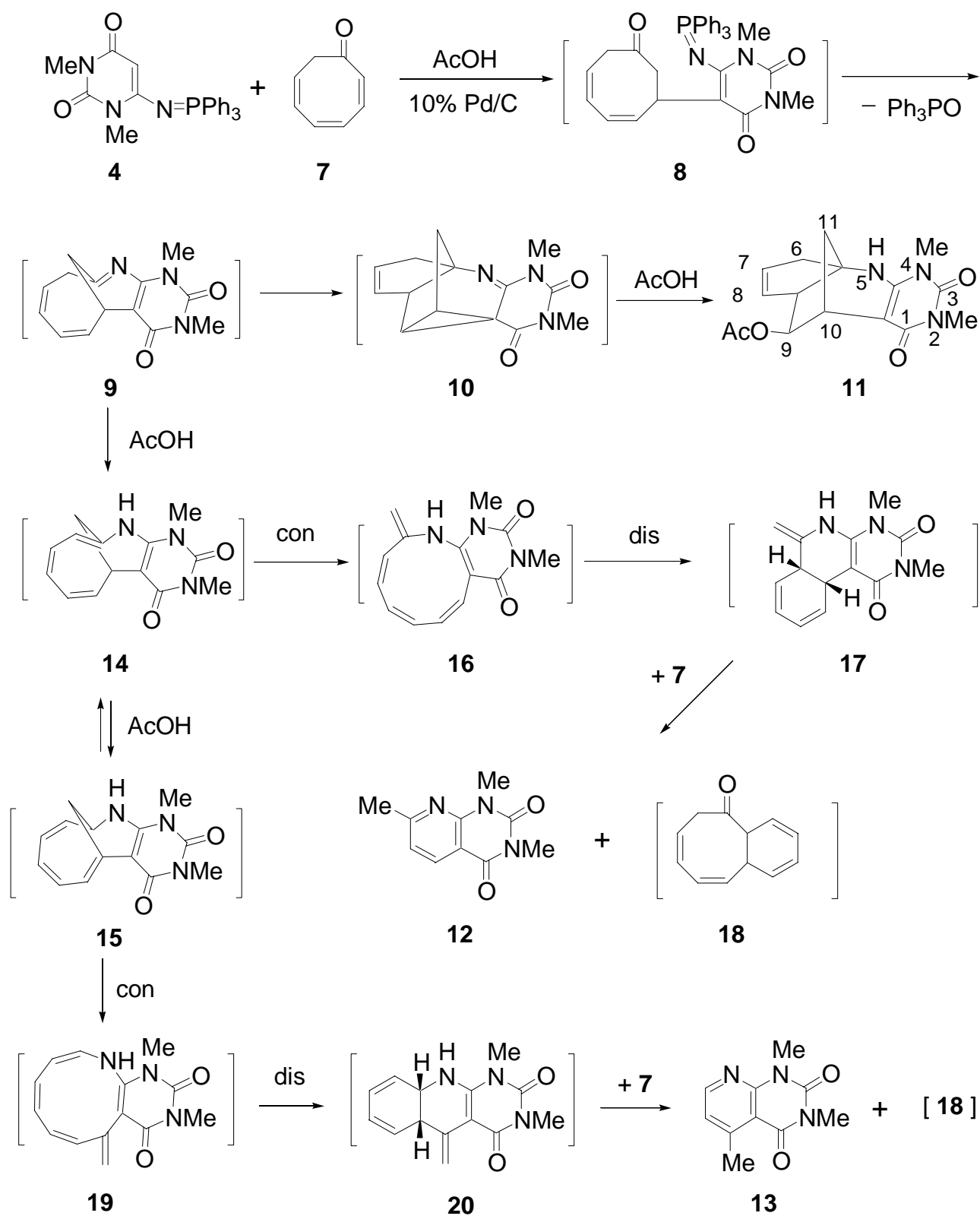
Scheme 2.

Similarly, the reaction of 6-amino-1,3-dimethyluracil (**5**)[19] with **7** in the presence of 10% Pd/C proceeded to afford the products (**11**), along with **12** and **13** (Scheme 3, Table 1, Entry 3)).   On the other hand, the reaction did not proceed in refluxing dioxane even after prolonged reaction time (Table 1, Entry 4).

Table 1. Results for the reactions of uracils (**4**)-(**6**) with 2,4,6-cyclooctatrienone (**7**)

Entry	Uracil	Ratio of **7/4-6**	Reaction conditions[a]		Product (Yield/%)[c]
			Solvent	Time/h	
1	**4**	1.5	AcOH	60	**11** (21), **12** (6), **13** (4)
2	**4**	1.2	Xylene	66	---[b]
3	**5**	1.5	AcOH	24	**11** (10), **12** (11), **13** (5)
4	**5**	1.2	Dioxane	48	**5** (81), **7** (94)
5	**6**	2.0	AcOH	20	**26** (15), **27** (18), **28** (12)

a. All the reactions were carried out in the presence of a dehydrogenating agent (10% Pd/C) under reflux.

b. Only decompositions of compounds (**4**) and (**7**) were observed.

In the reaction of **5** with **7**, however, the enamine alkylation of **5** to **7** and subsequent dehydration seem to give **14** as in the case of the reaction of **5** with 2-cyclooctenone, and not the more constrained **9**, which involves an azabutadiene-unit in a six-membered ring.[20] The compound (**14**) does not undergo dehydrogenation to afford **2b** (Scheme 1), but the protonation giving **21**, an intramolecular aza-Diels-Alder reaction, followed by AcO-incorporated ring-opening similar to those depicted in Scheme 2 results in the formation of product (**11**). On the other hand, the hydrogen migration of **14** in AcOH can realize equilibrium between **14** and **15**, which results in the formation of **12** and **13**, respectively, similarly to those depicted in Scheme 2.

On the other hand, the reaction of 3-methyl-6-methylminouracil (**6**)[21] with **7** proceeded as in the cases of compound (**5**). The enamine alkylation and dehydrating condensation gives **22**,[20] which undergoes hydrogen migration and protonation to yield **23** and **24**. The intermediate **24** undergoes intramolecular aza-Diels-Alder reaction and subsequent ring opening to afford the product (**26**). As in the cases of **14** and **15** (Scheme 2), the intermediates (**22**) and (**23**) undergo ring-opening and ring-closure sequences
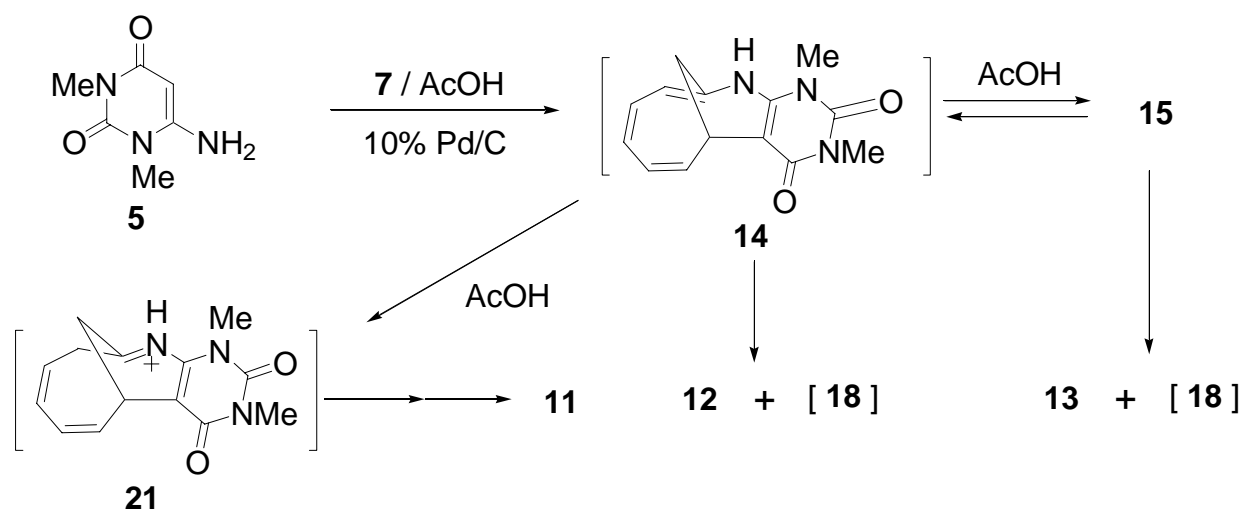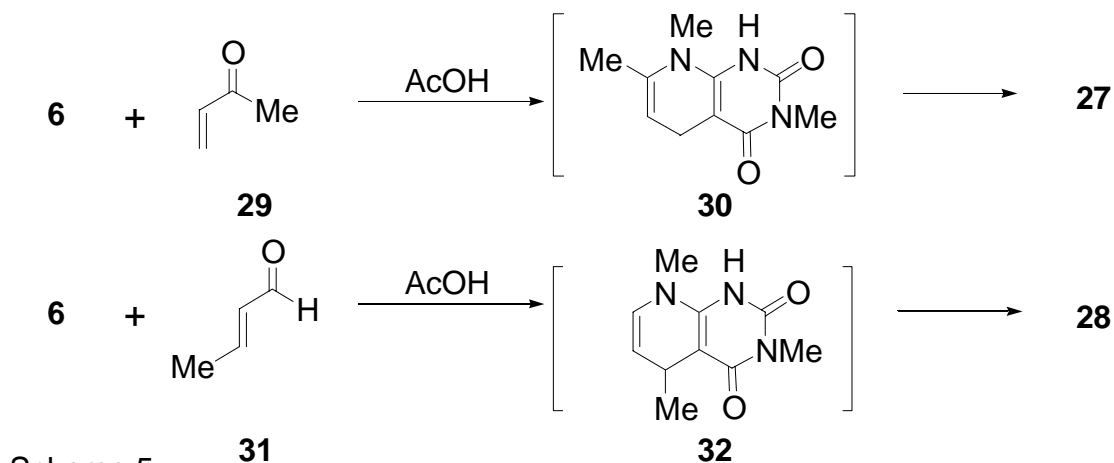

Scheme 3.
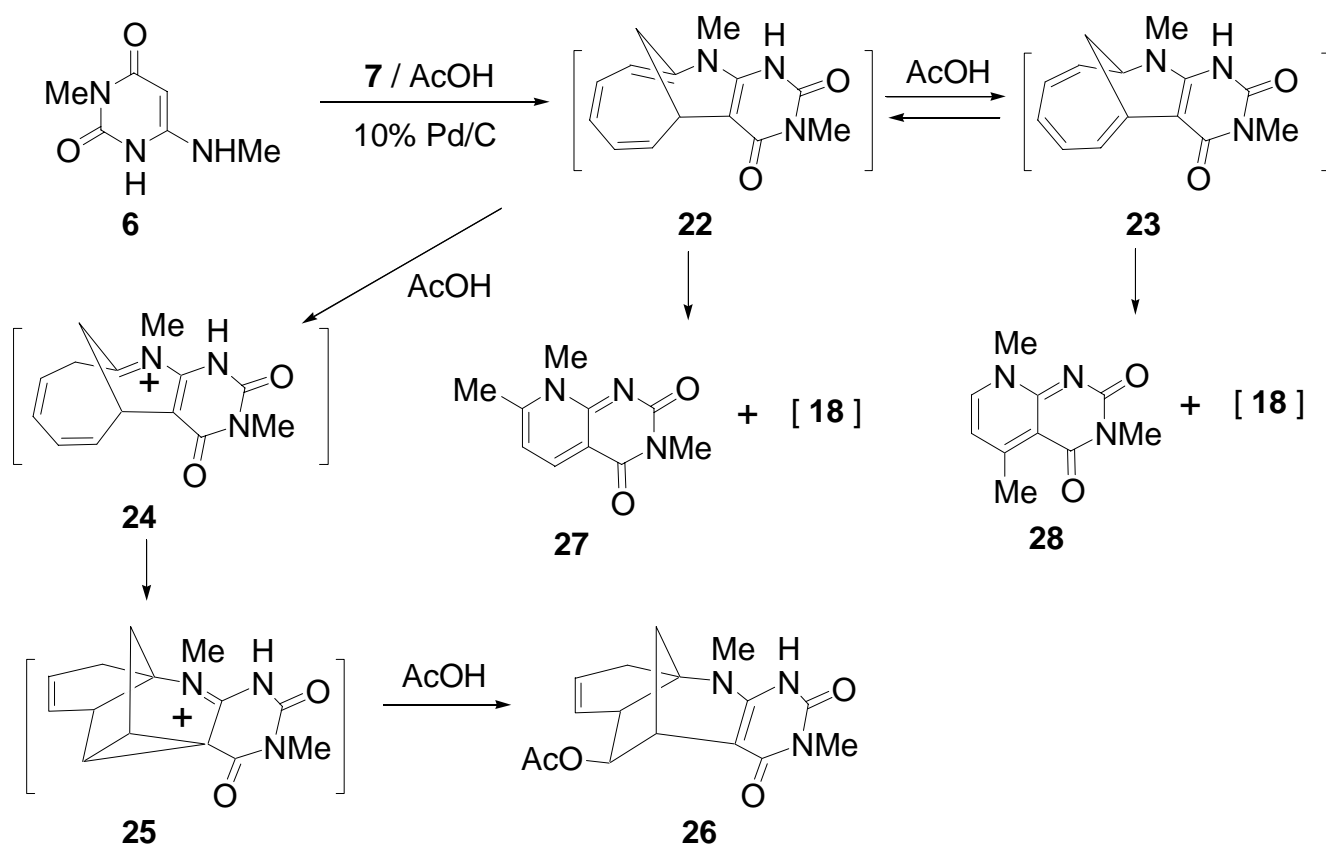
Scheme 4.

followed by Diels-Alder and retro-Diels-Alder reactions to result in the formation of 3,7,8- and 3,5,8-trimethylpyrido[2,3-*d*]pyrimidine-2(3*H*),4(8*H*)-diones (**27**) and (**28**).

The structure of compound (**26**) was confirmed from an inspection of the spectroscopic data including ^{1}H NMR, ^{13}C NMR and IR spectral data, as well as HRMS data. Comparison of the ^{1}H NMR spectral data of **26** with those of compound (**11**) is in good agreement with the proposed structure. Compounds (**27**) and (**28**) are new, and their structures are deduced from their spectral data, as well as independent syntheses. In a similar fashion to the pyridopyrimidine syntheses, [22-24] thermal reaction of **6** with 3-buten-2-one (**29**) as well as 2-butenal (**31**) in the presence of 10% Pd/C afforded **27** and **28**, respectively (Scheme 5). Their spectral data are in good accordance with those of the authentic specimen.

Scheme 5.

In summary, it is clarified that 6-phosphoranylideneaminouracil (**4**) and its related 6-aminouracils (**5**) and (**6**) react with an 8-membered ring compound, 2,4,6-cyclooctatrienone (**7**) to form constrained intermediates, uracil-annulated 8-azabicyclo[5.3.1]undeca-2,4,7,9-tetraene and 8-azabicyclo[5.3.1]undeca-2,4,6,9-tetraene derivatives. They are not converted to give π-systems such as **2b** and **3b** in the presence of 10% Pd/C, however, several interesting reactivities are found.

EXPERIMENTAL

IR spectra were recorded on a HORIBA FT-710 spectrophotometer. MS spectra and HRMS spectra were run on JMS-Automass 150 and JMS-SX102A spectrometers. Unless otherwise specified, ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a JNM-AL 400 and a AVANCE 600 spectrometers using $CDCl_3$ as the solvent, and the chemical shifts are given relative to internal $SiMe_4$ standard: *J*-values are given in Hz. Mps were recorded on a Yamato MP-21 apparatus and are uncorrected.

Reaction of 1,3-dimethyl-6-phosphoranylideneaminouracil (4) with 2,4,6-cyclooctatrienone (7) in AcOH. A mixture of **4** (125 mg, 0.3 mmol), **7** (54 mg, 4.5 mmol), and 10% Pd/C (5 mg) in AcOH (0.5 mL) was heated under reflux for 60 h. After the mixture was filtered through Celite and the solvent was evaporated, the residue was separated by TLC on silica ge (hexane-AcOEt : 1/1) to give the product (**11**) (20 mg, 21%) and a mixture of **12** and **13** in a ratio of 8/5. The results are summarized in Table 1 (Entry 1).

For *exo*-9-acetoxy-5a,10-methano-2,4-dimethyl-2*H*-5,5a,6,8a,9,10-hexahydrocyclopent[*b*]pyrimido[5,4-*f*]azepine-1,3(4*H*)-dione (**11**): colorless prisms; mp 200-201 °C (decomp) (from AcOEt); ^{1}H-NMR (400 MHz) δ 1.56 (1H, d, *J* = 11.2, H-11), 2.02 (3H, s, COMe), 2.14 (1H, dd, *J* = 11.2, 3.7, H-11), 2.45 (1H, dd, *J* = 16.6, 2.2, H-6), 2.76 (1H, dd, *J* = 16.6, 2.2, H-6), 3.32 (3H, s, Me), 3.34 (3H, s, Me), 3.37 (1H, d, *J* = 3.4, H-8a), 3.40-3.50 (1H, m, H-10), 4.65 (1H, br s, NH), 5.17 (1H, d, *J* = 6.8, H-8), 5.39 (1H, d, *J* = 3.4, H-9), 5.63 (1H, dd, *J* = 6.8, 2.2, H-7); ^{13}C NMR (150.9 MHz) δ 20.8, 28.0, 28.5, 33.7, 39.1, 40.5, 65.5, 70.0, 79.5, 88.5, 128.7, 129.6, 149.4, 151.4, 161.0, 170.4; IR (KBr) 1733, 1692, 1628 cm^{-1}; MS (EI) 317 (M$^+$, 38%), 258 (100); HRMS (FAB) Calcd for $C_{16}H_{20}N_3O_4$: 318.1455. Found: 318.1435 (M$^+$+1).

Reaction of 1,3-dimethyl-6-phosphoranylideneaminouracil (4) with 2,4,6-cyclooctatrienone (7) in xylene. A mixture of **4** (125 mg, 0.3 mmol), **7** (43 mg, 0.36 mmol), and 10% Pd/C (5 mg) in xylene (1 mL) was heated under reflux for 66 h. After the mixture was filtered through Celite and the solvent was evaporated, the residue was separated by TLC on silica gel (hexane-AcOEt : 1/1) to give no product except decomposition materials. The results are summarized in Table 1 (Entry 2).

Reaction of 6-amino-1,3-dimethyluracil (5) with 2,4,6-cyclooctatrienone (7) in AcOH. A mixture of **5** (33 mg, 0.2 mmol), **7** (38 mg, 0.3 mmol), and 10% Pd/C (5 mg) in AcOH (0.5 mL) was heated under reflux for 24 h. After the mixture was filtered through Celite and the AcOH was evaporated, the residue was separated by TLC on silica gel (hexane-AcOEt : 1/1) to give the products (**11**, **12**, and **13**). The results are summarized in Table 1 (Entry 3).

Reaction of 6-amino-1,3-dimethyluracil (5) with 2,4,6-cyclooctatrienone (7) in dioxane. A mixture of **5** (47 mg, 0.3 mmol), **7** (43 mg, 0.36 mmol), and 10% Pd/C (5 mg) in dioxane (1 mL) was heated under reflux for 48 h. After the mixture was filtered through Celite and the dioxane was evaporated, the residue was separated by TLC on silica gel (AcOEt) to give the starting materials. The results are summarized in Table 1 (Entry 4).

Reaction of 3-methyl-6-methylaminouracil (6) with 2,4,6-cyclooctatrienone (7) in AcOH. A mixture of **6** (47 mg, 0.3 mmol), **7** (72 mg, 0.6 mmol), and 10% Pd/C (5 mg) in AcOH (0.5 mL) was heated under reflux for 20 h. After the mixture was filtered through Celite and the solvent was evaporated, the resulting residue was purified through silica gel (AcOEt) to give the products (**26**, **27**,and **28**). The results are summarized in Table 1 (Entry 5).

For *exo*-9-acetoxy-5a,10-methano-2,5-dimethyl-2*H*-5,5a,6,8a,9,10-hexahydrocyclopent[*b*]pyrimido-[5,4-*f*]azepine-1,3(4*H*)-dione (**26**): colorless powder; mp 203-205 °C (from AcOEt); ^{1}H-NMR (600 MHz) δ 1.70 (1H, d, J = 11.5, H-11), 2.04 (3H, s, COMe), 2.06 (1H, dd, J = 11.5, 3.6, H-11), 2.56 (1H, dd, J = 16.8, 2.0, H-6), 2.88 (1H, dd, J = 16.8, 2.8, H-6), 3.01 (3H, s, Me), 3.30 (3H, s, Me), 3.31 (1H, d, J = 3.8, H-8a), 3.49-3.53 (1H, m, H-10), 5.17 (1H, d, J = 6.1, H-8), 5.37-5.41 (1H, m, H-9), 5.65 (1H, td, J = 6.1, 2.0, H-7), 10.30 (1H, br s, NH); ^{13}C NMR (150.9 MHz) δ 20.9, 27.0, 33.5, 33.7, 37.9, 38.6, 62.7, 75.1, 79.0, 90.9, 128.7, 128.9, 150.9, 152.7, 161.6, 170.4; IR (KBr) 1722, 1668, 1633 cm^{-1}; MS (EI) 317 (M$^+$, 23%), 258 (100); HRMS (FAB) Calcd for $C_{16}H_{20}N_3O_4$: 318.1455. Found: 318.1456 (M$^+$+1).

For 3,7,8-trimethylpyrido[2,3-*d*]pyrimidine-2(3*H*),4(8*H*)-diones (**27**)**:** yellow needles; mp 236-238 °C (from AcOEt); ^{1}H NMR (400 MHz) δ 2.65 (3H, s, Me), 3.44 (3H. s, Me), 3.99 (3H, s, Me), 6.72 (1H, d, J = 7.6, H-6), 8.42 (1H, d, J = 7.6, H-5); ^{13}C NMR (150.9 MHz) δ 22.2, 28.0, 34.7, 112.6, 113.6, 141.1, 154.6, 157.2, 157.3, 162.3; IR (KBr) 1690, 1640 cm^{-1}; MS (*m/z*) 205 (M$^+$, 3%), 149 (100). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.34; H, 5.03; N, 20.15.

For 3,5,8-trimethylpyrido[2,3-*d*]pyrimidine-2(3*H*),4(8*H*)-diones (**28**)**:** yellow powder; mp 236-238 °C (from AtOEt); ^{1}H NMR (400 MHz) δ 2.88 (3H, s, Me), 3.41 (3H, s, 3H, Me), 3.93 (3H, s, Me), 6.58 (1H, d, J = 6.8, H-6), 7.75 (1H, d, J = 6.8, H-7); ^{13}C NMR (150.9 MHz) δ 23.0, 27.9, 41.4, 113.3, 115.3, 142.1, 156.2, 156.9, 160.1, 163.1; IR (KBr) 1676, 1636 cm^{-1}; MS (m/z) 205 (M$^+$, 100%). Anal. Calcd for $C_{10}H_{11}N_3O_2 \cdot H_2O$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.83; H, 5.72; N, 18.65.

Independent Preparation of 3,5,8-Trimethylpyrido[2,3-*d*]pyrimidine-2,4(3*H*,8*H*)-dione (27) and 3,7,8-Trimethylpyrido[2,3-*d*]pyrimidine-2,4(3*H*,8*H*)-dione (28). A solution of 3-methyl-6-(methylamino)uracil **6** (115 mg, 1 mmol), 10% Pd/C (10 mg), and 3-butenone (**29**) (420 mg, 6 mmol) or 2-pentenal (**31**) (140 mg, 2 mmol) in AcOH (1 mL) was stirred at 85 °C for 7 h or 115 °C for 5 h. After the reaction was completed, the reaction mixture was concentrated *in vacuo* and the resulting residue was purified through columun chromatography on silica gel by using AcOEt as the eluent to give the products (**27**) (40%) or (**28**) (57%), which are identical with the authentic specimens.

Crystal structure determination of compound (11)

Single crystals of **11** were recrystallised from AcOEt. **Crystal data:** $C_{16}H_{19}N_3O_4$, M = 317.35, monoclinic, a = 11.5906(0), b = 13.2325(0), c = 10.5562(0) Å, β = 109.368(0) °, U = 1527.40(0) Å^3, T = 240 K, space group $P2_1/a$ (no. 14), Z = 4, μ(Cu-Kα) = 0.5952 mm^{-1}, 3344 reflections measured, 2860 unique (R_{int} = 0.147). The final $R(F^2)$ and $wR(F^2)$ were 0.057 and 0.075 for 2753 observed reflections $[F^2 > 2\sigma(F^2)]$ used in all calculations.[25]
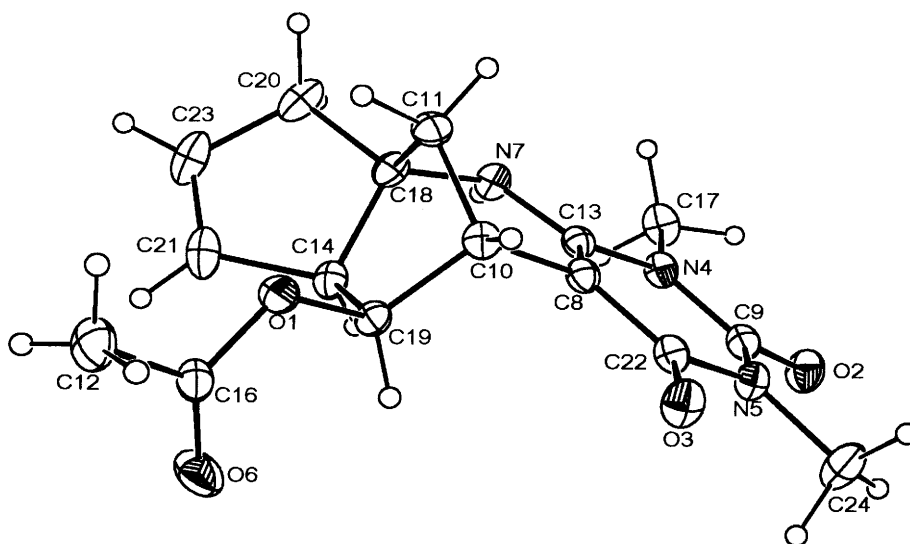

Figure 1.   The ORTEP drawing of the molecular structure of **11** as 30% probability ellipsoids

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