Reactions of Uracils. 21.[1] Zwitterionic Heteropolycyclic Uracils by a Novel Three-Component Reaction: Iminophosphorane, Isocyanate, Heteroarene

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The novel three-component reaction of (uracil-6-ylimino)phosphorane **1**, isocyanate **2**, and (substituted) pyridines gives, in a one-pot procedure, a variety of new pyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidines **3-11**. The zwitterionic ground state of these new ring systems is *i.a.* established by means of solvatochromism, Hammett correlations, NMR, and X-ray analysis. Replacement of the pyridine by isoquinoline and phthalazine gives access to the novel ring systems pyrimido[4′,5′:4,5]pyrimido-[6,1-*a*]isoquinoline and -phthalazine, which are formed as dihydro derivatives (**14, 15**) or as zwitterions (**13, 17**), depending on the reaction conditions. Oxidative cleavage of the phthalazine **15** in nitrobenzene affords the pyrimido[4,5-*d*]pyrimidines **16**.

In the course of our studies concerning the synthetic potential of the iminophosphoranes[1] of heterocyclic β-enamino esters[3] and uracils,[4] we previously reported a novel type of three component reaction [(uracil-6-ylimino)-phosphorane/pyridine/isocyanate)] leading to hitherto unknown heterocondensed zwitterionic uracils.[5] This heteroannulation involves an initial aza-Wittig reaction of the iminophosphorane with isocyanate. The resulting intermediary uracilylcarbodiimide, a special kind of vinylic heterocumulene, readily undergoes addition to pyridine, followed by a cyclization/oxidation sequence. Although vinylic carbodiimides are well-documented in the literature,[6] very few of their [4 + 2]-cycloadditions have been reported[7] and only one publication has dealt with pyridine as the dienophile.[8] Furthermore, a quantitative colorimetric analysis for carbodiimides has been developed, which is based on the cleavage of pyridine with CN^+ (König reaction) and related species.[9]

Continuing our investigations of the synthetic utility and mechanism of this three-component reaction, we have discovered that a surprisingly broad range of different heteroarenes and isocyanates can be employed successfully. Thus, this reaction provides versatile access to novel tri- and tetracyclic systems. Given the reports on the biological activities of related isomeric heterocycles,[10] these new compounds may provide potential new leads. The zwitterionic ground states of heterocyclic systems have hitherto received little attention;[11] this roused our interest in studying the spectral features of these systems.

Results and Discussion

Reactions with Pyridines. Treatment of 6-[(triphenylphosphoranylidene)amino]uracil **1**, easily produced from 6-aminouracil and *in situ*-generated dihalogenotriphenylphosphorane,[4b] with isocyanates in excess pyridine led to the intensely colored novel ring system pyrido-[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine **3** (Scheme I). Using phenyl isocyanate **2a**, the tricycle **3a** was smoothly formed, the structure of which has already been established by a single crystal X-ray analysis.[5]

A wide variety of heteroarenes and isocyanates readily underwent this three-component reaction (Scheme II). Thus, upon heating without additional solvent, (uracil-6-ylimino)phosphorane **1**, the isocyanates **2**, and ethyl nicotinate yielded regioselectively the orange-colored tricyclic 9-carboxylates **4**. No traces of the energetically disfavored 11-carboxylate could be isolated, whose substitution pattern would cause nonplanarity[12] and reduced p-overlap. Under analogous conditions, methyl isonico-

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(1) Part 20: Wamhoff, H.; Schmidt, A. Heterocycles **1993**, *35*, 1055. At the same time part 28 of the series: Dihalogentriphenylphosphoranes in Heterocyclic Synthesis; part 27: Wamhoff, H.; Kroth, E.; Strauch, C. *Synthesis* **1993**, 1129.

(2) Based in part on Diplomarbeit and Dissertation A. Schmidt, Universität Bonn, 1990-1992. Present address: Institut für Organische Chemie, Soldtmannstrasse 16, D-17489 Greifswald.

(3) Reviews and recent publications in this area, see: (a) Wamhoff, H. *Adv. Heterocycl. Chem.* **1985**, *38*, 299. (b) Wamhoff, H. In *Lectures in Heterocyclic Chemistry*; Castle, R. N., Schneller, S. W., Eds.; Heterocorporation: Orem/Utah, 1980; Vol. V, pp 61ff. (c) Wamhoff, H.; Berressem, R.; Herrmann, S. *Synthesis* **1993**, 107. (d) Wamhoff, H.; Herrmann, S.; Stölben, S.; Nieger, M. *Tetrahedron* **1993**, *49*, 581.

(4) (a) Review: Wamhoff, H.; Dzenis, J.; Hirota, K. *Adv. Heterocycl. Chem.* **1992**, *55*, 129. (b) Wamhoff, H.; Schupp, W.; Kirfel, A.; Will, G. *J. Org. Chem.* **1986**, *51*, 149. (c) Wamhoff, H.; Schupp, W. *J. Org. Chem.* **1986**, *51*, 2787. (d) Wamhoff, H.; Walsh, E. B. *Chem. Ber.* **1989**, *122*, 1673. (e) Walsh, E. B.; Nai-jue, Z.; Fang, G.; Wamhoff, H. *Tetrahedron Lett.* **1988**, *29*, 4401. (f) Wamhoff, H.; Muhr, J. *Synthesis* **1988**, 919.

(5) Wamhoff, H., Schmidt, A. *Tetrahedron Lett.* **1991**, 4373.

(6) See, for example: (a) Nitta, M., Soeda, H.; Koyama, S.; Ino, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1325. (b) Goerdeler, J.; Raddatz, S. *Chem. Ber.* **1980**, *113*, 1095. (c) Zimmermann, D. M.; Olofson, R. A. *Tetrahedron Lett.* **1970**, 3453. (d) Kurzer, F.; Douraghi-Zadeh, K. *Chem. Rev.* **1967**, *67*, 107. (e) Williams, A.; Ibrahim, I. T. *Chem. Rev.* **1981**, *81*, 589. (f) Saito, T.; Nakane, M.; Endo, M.; Yamashita, H.; Oyamada, Y.; Motoki, S. *Chem. Lett.* **1986**, 135. (g) Dondoni, A. *Heterocycles* **1980**, *14*, 1547.

(7) (a) Goerdeler, J.; Lohmann, H. *Chem. Ber.* **1977**, *110*, 2996. (b) Noguchi, M. J. *Heterocycl. Chem.* **1991**, *4*, 885. (c) v. Giszycki, U.; Oertel, G. *Angew. Chem.* **1968**, *80*, 363. (d) Bödeker, J.; Köckritz, P.; Kraft, R. *Z. Chem.* **1977**, *17*, 371. (e) Bödeker, J.; Courault, K.; Köckritz, P. *Ibid.* **1980**, *20*, 211. (f) Bödeker, J.; Köckritz, P. *Ibid.* **1982**, *22*, 140. (g) Bödeker, J.; Courault, K. *Tetrahedron* **1978**, *34*, 101. (h) Sakamoto, M.; Miyazawa, K. Tomimatsu, T. *Chem. Pharm. Bull.* **1976**, *24*, 2532.

(8) Arbusov, B. A.; Zobova, N. N. *Synthesis* **1982**, 433.

(9) Wilchek, M.; Miron, T.; Kohn, J. *Anal. Biochem.* **1981**, *114*, 419.

(10) (a) Frei, J.; Schweizer, E. (Ciba Geigy AG) Eur. Pat. Appl EP 46,446 (Cl. C07D487/04), 24 Feb 1982, CH Appl. 80/6,197, 15 Aug 1980; *Chem. Abstr.* **1982**, *96*, 217872. (b) Friary, R. J.; Siegel, M. I.; Smith, S. R. (Schering Corp.) PCT Int. Appl. WO 86 06,375 (Cl. C07D471/14), 06 Nov 1986, US Appl. 729,334, 01 May 1985; *Chem. Abstr.* **1987**, *107*, 7208.

(11) For some examples and discussions, c.f. Huisgen, R. *Angew. Chem.* **1963**, *13*, 604 and literature cited therein.

(12) (a) For X-ray analyses and resolution of isogeometric chiral helices, see: (a) Hirschfeld, F. L.; Sandler, S.; Schmidt, G. M. J. *J. Chem. Soc.* **1963**, 2108. (b) Newman, M. S.; Wheatley, W. B. *J. Am. Chem. Soc.* **1948**, *70*, 1913. (c) Newman, M. S.; Mentzer, R. G.; Slomp, G. *Ibid.* **1963**, *85*, 4018.

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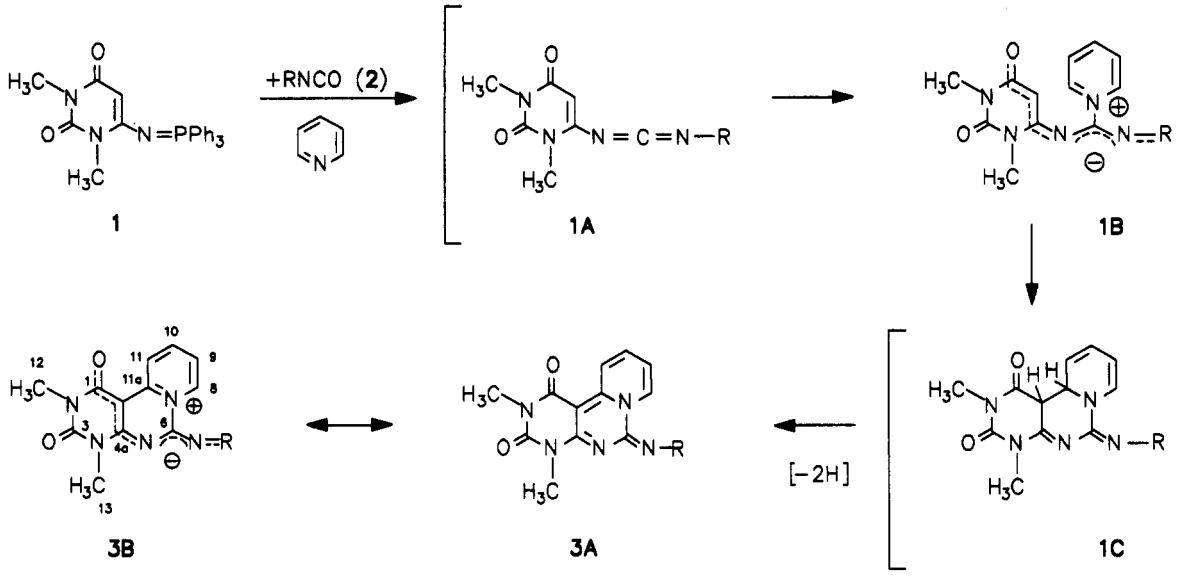
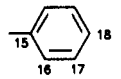
Scheme I



a: R= 

b: R= 4-C_6H_4Cl

c: R= 3-$C_6H_4CF_3$

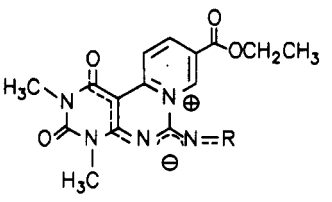
e: R= -*i*Pr

f: R= 4-$C_6H_4NO_2$

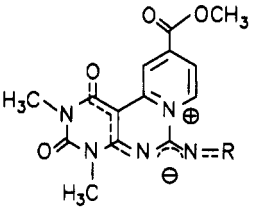
g: R= $-SO_2C_6H_4CH_3$

h: R= $-CH_2CH=CH_2$

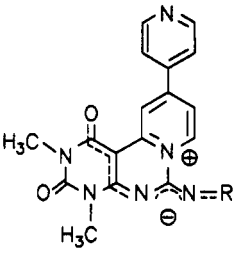
Scheme II



4a–d



5a–c



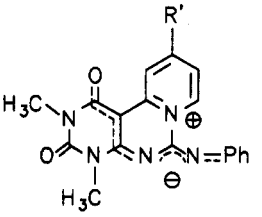
9a–d

a: R= C_6H_5

b: R= 4-C_6H_4Cl

c: R= 3-$C_6H_4CF_3$

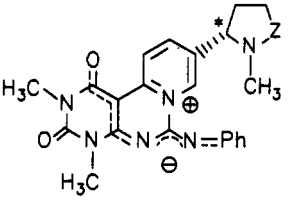
d: R= 4-$C_6H_4CH_3$



6: R'= $-COCH_3$

7: R'= $-CH_3$

8: R'= $-CH_2CH_2$- 



10: Z= $-CH_2-$

11: Z= $-CO-$

tinate and 4-acetylpyridine gave the red-colored tricycles **5** and **6**, respectively. A similar reaction was observed with 4-picoline and 1,2-di(4-pyridinyl)ethane which formed the yellow heterocycles **7** and **8**, respectively. Furthermore, simple annulation of 4,4′-bipyridine in absolute acetonitrile resulted in the formation of pale red, amorphous precipitates **9**, which might be of biological interest due to their close relationship to a class of well-known and widely used herbicides.[13] These results prompted us to replace pyridine with naturally occurring pyridine alkaloids. Thus, employing (−)-nicotine and its oxidative metabolite (−)-cotinine in this reaction regioselectively afforded the pyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine **10** in 30% ee {$[\alpha]_D = -4.5°$ (c = 1.4 in CH_2Cl_2)} and the alkaloid **11** {$[\alpha]_D$

(13) Dodge, A. D. *Endeavour* **1970**, *111*, 130.

Table I. Negative Solvatochromism of 3a[a]

solvent	E_T[c]	λ (log ε)
CH_2Cl_2	0.321	≈565, 420 (3.77), 342 (4.18)
MeOH	0.765	≈550, 408, 336[b]
CF_3CH_2OH	0.889	≈535, (2.27), 399 (3.78), 333 (3.81)
AcOH	0.648	≈530, 377, 326[b]

[a] Further results are given in the Experimental Section. [b] Qualitative measurement due to limited solubility. [c] See ref 17.

= +9.1° (c = 0.8 in CH_2Cl_2)}, respectively. However, purification of the crude products **8**, **10**, and **11** turned out to be rather difficult. The enantiomeric excess of **10** could be determined by ^1H NMR in the presence of Eu(hfc)$_3$. However, this measurement failed in the case of **11**, due to signal overlap of the alkaloid with the shift reagent.

The majority of the zwitterions **3-11** were very stable, almost completely unreactive, and of rather limited solubility in common solvents.

Although many different pyridines could be successfully employed in this three-component reaction, a principle limitation seems to be the failure of pyridines carrying strongly basic (e.g. DMAP) or α-substituents, most likely the result of interaction with the intermediary carbodiimide and steric hindrance, respectively.

Zwitterionic Ground State. The aforementioned heterocyclic systems can be represented by several possible Lewis structures, and only one is uncharged. If the structure is assumed to be a weighted average of them, a high degree of charge separation in the ground state can be expected. This was in fact supported by all spectroscopic data. Since it is known that the delocalization of the negative charge in betaines is the most important criterion for stability,[14] our systems might be best represented by the canonical formula **3B** rather than by the nonpolar structure **3A**.

Firstly, the well-documented effect of negative solvatochromism is considered to be an important indicator of a zwitterionic ground state.[15] Consistent with reported ylides[14] and mesomeric betaines,[16] all UV-vis absorption maxima are shifted with increasing polarity of the solvent (characterized e.g. by the dimensionless E_T scale[17]) to shorter wavelengths (Table I). According to observations of Kosower *et al.*, the excitation HOMO-LUMO causes a charge neutralization and decreases the dipole moment.[18] Thus, in the case of zwitterionic molecules, the electronic excitation is facilitated by nonpolar solvents and, as a consequence, a negative solvatochromism is observed. By contrast, using acetic acid as solvent, the zwitterion **3a** is additionally stabilized by hydrogen bonding and a very strong hypsochromic shift of the absorption maxima is observed.

Secondly, the dipolar ground state is further supported by means of Hammett correlations[18] in a specific example of a linear free energy relationship.[15e] According to Kosower *et al.* and Reichardt *et al.* the spectroscopic Hammett equation can be expressed as follows:

$$(E_{T,R} - E_{T,0})/2.303RT = \sigma\rho_A \qquad (1)$$

where $E_{T,R}$ and $E_{T,0}$ are the transition energies of the substituted and the reference compound **3a** (R = H), respectively, σ is the Hammett constant,[20] R is the gas constant, T is the temperature, and ρ_A ("absorption constant"[18]) is the slope of the line. Our results are presented in Table II and are shown graphically in Figure 1.

In accordance with eq 1, the differences $E_{T,R} - E_{T,0}$ are a linear function of the σ_m and σ_p constants of suitable model substituents. But 9-ethyl carboxylate substitution

Table II. Results of the Spectroscopic Hammett Equation (eq 1)

compd	λ[a] (nm)	E_T[b] (kJ/mol)	$\frac{E_{T,R}-E_{T,0}}{2.303RT}$	σ[c,d]
7	395	302.84	+3.16	−0.17 (σ_p Me)
8	410	291.76	+1.22	−0.15 (σ_p Et)
10	418	286.18	+0.24	−0.07 (σ_m iPr)
3a	420	284.81	0	0
11	425	281.46	−0.58	−0.07 (σ_m iPr)
5a	470	254.51	−5.31	+0.45 (σ_p COOMe)
6	485	246.64	−6.68	+0.50 (σ_p COMe)

[a] π–π* absorption. [b] $E_T = N_L hc\tilde{\nu}$. [c] Model substituents used and their σ constants in parentheses. [d] To the best of our knowledge, the σ constant of the 4-pyridine substituent (cf. **9a**) is unknown. [e] Modified excitation energy of the 9-ethyl carboxylate substituent is 4.63.

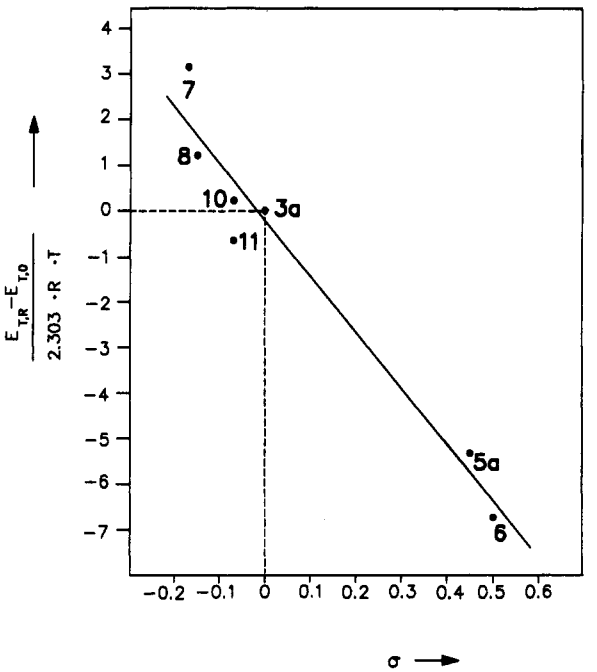


Figure 1. Hammett correlation. Modified excitation energies *vs* σ constants.

(14) (a) Surpateanu, G.; Catteau, J. P.; Karafiloglou, P.; Lablache-Combier, A. *Tetrahedron* **1976**, *32*, 2647. (b) Zugravescu, I.; Petrovanu, M. *N-Ylid-Chemistry*, McGraw Hill International Book Co.; Bucharest, 1976. (c) Kröhnke, F. *J. Am. Chem. Soc.* **1953**, *65*, 605.

(15) (a) Kosower, E. M. *J. Am. Chem. Soc.* **1958**, *80*, 3253. (b) Kosower, E.M.; Ramsey, B. G. *J. Am. Chem. Soc.* **1959**, *81*, 856. (c) Boyd, G. V. *Tetrahedron Lett.* **1966**, 3369. (d) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; Verlag Chemie: Weinheim, 1988. (e) Reichardt, C. *Angew. Chem.* **1979**, *91*, 119. (f) Liptay, W. *Angew. Chem.* **1969**, *81*, 195. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 177. (g) Stafford, W. H. *J. Chem. Soc.* **1952**, 580.

(16) (a) Potts, K.; Murphy, P. M.; Kuehnling, W. R. *J. Org. Chem.* **1988**, *53*, 2889. (b) Potts, K.; Murphy, P. M.; DeLuca, M. R., Kuehnling, W. R. *Ibid.* 2898. (c) Gotthardt, H.; Kinzelmann, H.-G. *Chem. Ber.* **1986**, *119*, 2308.

(17) For conversion of the $E_T(30)$ values into the E_T scale, see: Reichardt, C.; Harbusch-Görnert, E. *Liebigs Ann. Chem.* **1983**, 721. For "Z"-values, cf. lit.[15a]

(18) Reichardt, C.; Müller, R. *Liebigs Ann. Chem.* **1976**, *11*, 125 and literature cited therein.

(19) Kosower, E. M.; Hoffmann, D.; Wallenfels, K. *J. Am. Chem. Soc.* **1962**, *84*, 2755.

(20) (a) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207. (b) McDaniel, D. H.; Brown, H. C. *J. Org. Chem.* **1958**, *23*, 420. (c) Jaffé, H. H. *Chem. Rev.* **1953**, *53*, 191.

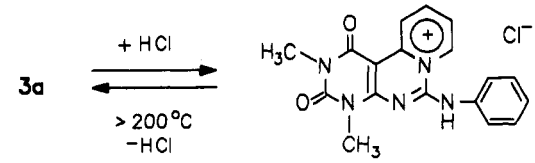
(4a) formed the strongly stabilizing β-enamino carbonyl chromophore (N(7)—C(8)—C(9)—C=O; "push-pull resonance"[3]), which gave rise to a widely divergent point. After omitting this value, the regression line corresponded to the equation $f(\sigma) = -12.24\sigma - 0.27$; the data pairs yielded a correlation coefficient $r = -0.979$ and thus indicated a fair fit with linearity.[20c] Similar to several studies of Reichardt *et al.* on zwitterionic pyridinium phenolates,[18] a characteristic negative slope ($\rho_A = -12.24$) was found, thus indicating an increasing charge density at the substituted pyridinium atoms (C-9, C-10) during excitation.

As a further consequence, electron-withdrawing substituents on the pyridine unit, while facilitating the charge transfer by increasing the electron affinity of this acceptor segment, caused a bathochromic shift of the absorption. *Vice versa*, electron-donating substituents induced a hypsochromic shift. Thus, replacement of the 10-methyl with a 10-acetyl group changed the color from intensively yellow to dark red. The corresponding excitation energy difference is 48 kJ/mol.

The results of the single crystal X-ray analysis[5] were as follows: In contrast to our previous results concerning zwitterionic amidinium pyridinedionates[4b] whose charged segments were twisted, compound **3a** was planar [torsion angle at N(7): 0.00°]. But similar to several pyridinium derivatives,[21] the C(6)–N(7) bond length [147.5(4) pm] was increased relative to a C_{sp^2}–N_{sp^2} bond. Obviously, there is no π-interaction between the pyridinium unit and C(6), and the charges are separated by a single bond. In contrast to this, the bonding C(11a)–C(11b) [142.2(4) pm] has some π-contributions and stabilizes the system.[14a] As a consequence of the dipolarity, **3a** crystallizes in its elemental cell in an alternating head-to-tail orientation. Despite the absence of hydrogen bonding, the crystal is of high density (1.443 g cm^{-3}) and has a high melting point (211 °C).[5]

The NMR spectra should reveal something about the electron distribution in our compounds. The zwitterionic character causes downfield shifts of the pyridine-H resonances and enlarged coupling constants. In the case of 11-H, this shift was further intensified by the anisotropic effects of the carbonyl moiety. In compounds **3**-**11**, the ^{1}H NMR signals of 8-H were observed in the region of δ 9.50–10.27 ppm (^3J(H,H) = 7.4–9.0 Hz), of 9-H in the region of δ 7.82–8.12 ppm (exception is **7**: δ 7.11 ppm due to the inductive effect of the methyl group), and of 11-H in the region of δ 9.47–9.85 ppm (^3J(H,H) = 8.4–10.0 Hz). The ^{13}C NMR signals of **3a** could be assigned as follows: the C-8 signal appeared at δ 132.86 ppm with a very large $^1J_{CH}$ coupling constant (191.7 Hz). In agreement with previous results concerning the effects of substituents upon the chemical shifts of pyridinium betaines and related compounds,[22] the signal for C-9 was found at δ 118.76 ppm ($^1J_{CH}$ = 172.8 Hz). Because of the strong electron-donation of the enamine substructure of uracil, as evidenced by PES spectra and calculations,[23] the C-11b of **3a** induces this considerable upfield shift. The signals of C-10 and C-11 are observed at δ 141.26 ppm ($^1J_{CH}$ = 168.3 Hz) and 122.70 ppm ($^1J_{CH}$ = 177.3 Hz), respectively. These assignments were further confirmed by a ^{13}C–^{1}H correlation of **11**, the most soluble compound of the series. Due to the rather limited solubility, all efforts to obtain ^{15}N NMR data failed.

Scheme III



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The betaine **3a** reacted quantitatively with concentrated hydrochloric acid to form an insoluble pale yellow salt **12** [M^+ *m/z* 334 (100%)] which decomposed upon treatment with base or heating (200 °C) in HCl and **3a** [M^+ 333 (100%)] (Scheme III). One marked effect on the chemical shifts that originated in the change from betaine to salt was the downfield shift of 10-H to 8.42 ppm (now "C-4" of a pyridinium ion; $\Delta\delta \approx 1.1$ ppm) and the appearance of an additional broad signal at 5.00 ppm. Accordingly, a broad NH or OH absorption band was observed in the range of 2900–3100 cm^{-1}, so that no exact assignment of the protonation site could be made.

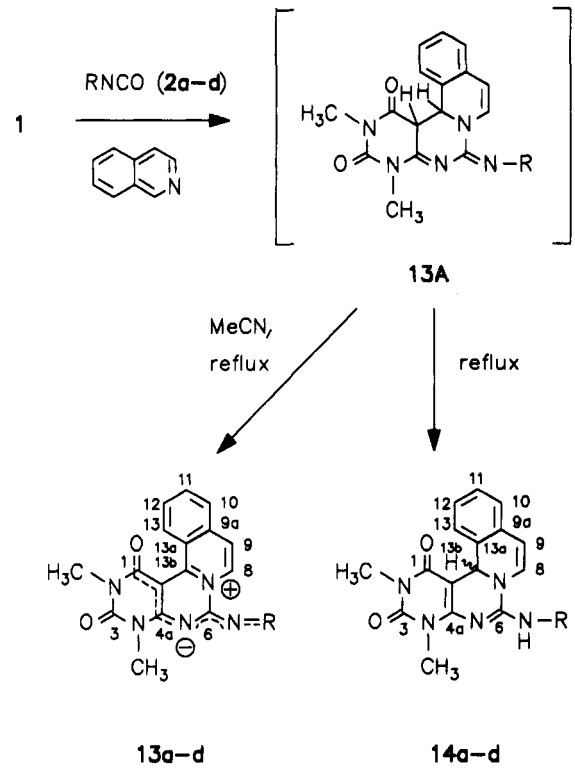
Mechanistic Comments. Course and outcome of the three-component reaction were influenced by the basicity and by the electronic effects of the substituents, as well as by the reactivity of the isocyanate. As the basicity and the Hammett's σ constants are competing parameters, we assume a stepwise mechanism as depicted in Scheme I: Initial aza-Wittig reaction of the (uracil-6-ylimino)phosphorane **1** with the isocyanate **2** yields a nonisolable uracilylcarbodiimide **1A**. In accordance with some calculations on model compounds,[23,24] this can be characterized as an *enamine carbodiimide* with a considerable readiness toward [4 + 2]-cycloadditions.

Subsequent addition of pyridine leads most probably to an intermediary 1,6-dipolar pyridinium C-ylide **1B**. According to reports concerning the well-known Menschutkin reaction,[25] this addition should be accelerated by a strongly basic heteroarene. This is indeed confirmed by the following simple experiment: Treatment of the (uracil-6-ylimino)phosphorane **1** with phenyl isocyanate **2a** in an equimolar mixture of pyridine (pK_a 5.25) and 4-picoline (pK_a 6.03) yields exclusively **7** in 50% yield. No traces of **3a** (formed by addition of the less basic pyridine) were detectable by ^{1}H NMR.

Furthermore, the cyclization step **1B** to **1C** should be facilitated by increasing the electron affinity of the pyridinium segment. Thus, intensifying the 1,6-dipolarity, which is *i.a.* due to the well-known enamine functional substructure in the 5,6-double bond region of uracil,[23] by substituting the pyridine moiety with electron-withdrawing substituents should accelerate the cyclization step. Indeed, ethyl nicotinate [σ_p (COOEt) = +0.45; pK_a 3.35] smoothly forms **4**, whereas 3-picoline [σ_p (Me) = −0.17, pK_a 5.68] leads to intractable reaction mixtures. Moreover, an equimolar mixture of ethyl nicotinate and pyridine yields a 4.5:1 mixture of **3a**/**4a**, indicating that reduced

(21) E.g., see refs 14a and 16, and (a) Camerman, A. *Can. J. Chem.* **1970**, *48*, 179. (b) Truter, M. *J. Chem. Soc.* **1960**, 997.
(22) Takeuchi, Y.; Dennis, N. *Org. Magn. Reson.* **1976**, *8*, 21.
(23) Lauer, G.; Schäfer, W.; Schweig, A. *Tetrahedron Lett.* **1975**, 3939.
(24) See ref 4d, and Nitta, M.; Soeda, H.; Koyama, S.; Iino, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1325.
(25) Clarke, H.; Rothwell, K. *J. Chem. Soc.* **1960**, 1885.
(26) van Veldhuizen, A.; van Dijk, M.; Sanders, G. M. *Org. Magn. Reson.* **1980**, *13*, 105.

Scheme IV



a: R= C_6H_5 c: R= 3-$C_6H_4CF_3$

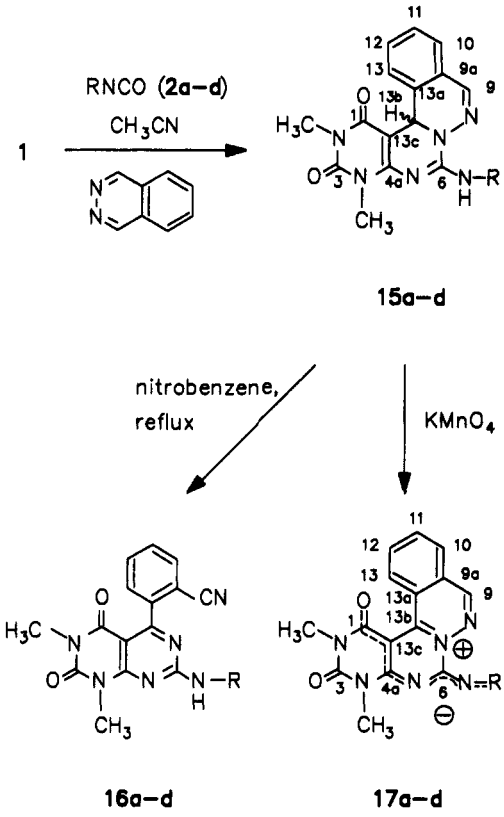
b: R= 4-C_6H_4Cl d: R= 4-$C_6H_4CH_3$

basicity may be partially compensated for by an electron-withdrawing substituent.

In our opinion, these experimental results lend strong support for the mechanism proposed.

Isoquinoline. Accordingly, isoquinoline employed as the heteroarene component gave the novel ring system pyrimido[4′,5′:4,5]pyrimido[6,1-*a*]isoquinoline (Scheme IV). Surprisingly, the outcome of the reaction was seriously dependent on the reaction conditions used. The one-pot procedure without additional solvent, as was applied to the pyridine series, yielded the zwitterionic yellow to amber colored species **13** [e.g. **13a**: M^+ 383 mmu (100%)]. However, upon using absolute acetonitrile as solvent, the final oxidation step failed. Instead, 1,5-H shift of the intermediary dihydro derivative **13A** resulted in the formation of the 1*H*,2*H*-isoquino[2′,1′:3,4]pyrimido-[4,5-*d*]pyrimidine **14** [e.g. **14a**: M^+ 385 (85%), υ_{NH} 3325 cm^{-1}, δ 5.58 ppm (s, 1, 13b-H)]. Both **13** and **14** displayed a rather limited solubility so that detailed spectroscopic examinations were precluded. However, in contrast to the nearly colorless dihydro derivatives **14**, whose heteroaromatic resonances were found in the range of δ 6.51–7.44 ppm, the corresponding signals of **13** were shifted to significantly lower field, similar to the pyridine zwitterions described before. Thus, depending on the substitution pattern, the signals of 8-H were observed at δ 9.43–8.73 ppm, of 13-H at δ 8.40–7.82 ppm and of 11-H at δ 7.80–7.70 ppm. The ^3J(H,H) values are typically enlarged (J = 7.0–8.0 Hz). Comparing the ^{13}C resonances of **13b** with **14a** (each the most soluble of the series), we obtained evidence for the different charge distributions in the two systems. In full agreement with the pyridine zwitterions, C-9 of **13** is shifted considerably upfield ($\Delta\delta$ = −5.1 ppm), whereas

Scheme V



a: R= C_6H_5 c: R= 3-$C_6H_4CF_3$

b: R= 4-C_6H_4Cl d: R= 4-$C_6H_4CH_3$

C-11 ($\Delta\delta$ = +7.0 ppm) and C-13 ($\Delta\delta$ = +8 ppm) were deshielded. Although confined to a very limited range of solvent polarity, compound **13a** was found to be negatively solvatochromic [UV-vis (CH_2Cl_2) (E_T = 0.321) λ 540, 450, 350 nm; UV-vis (MeCN) (E_T = 0.472) λ 530, 440, 345 nm].

Phthalazine. Upon variation of the three-component reaction to (uracil-6-ylimino)phosphorane, isocyanate, and phthalazine, the novel ring system 1*H*,2*H*-phthalazino[2′,1′:3,4]pyrimido[4,5-*d*]pyrimidine **15** was formed smoothly in moderate to very good yields [e.g. **15a**: M^+ m/z 386 mmu (86%), υ_{NH} 3345 cm^{-1}, δ 5.62 ppm (d, 1, 13b-H), 8.12 ppm (s, broad, 1, NH)] (Scheme V). Due to the high melting point of phthalazine (90–91 °C), this reaction required absolute acetonitrile as solvent. Upon heating **15** in nitrobenzene (200 °C) (a well-known aromatization reaction[4d,e]), nearly insoluble grey precipitates were formed in excellent yield. The spectroscopic features of these compounds (e.g. **16a**: M^+ m/z 384 mmu (78%), υ_{CN} 2220 cm^{-1}, υ_{NH} 3355 cm^{-1}) were consistent with the hitherto unknown 2′-cyanophenyl-substituted pyrimido[4,5-*d*]pyrimidines **16**, obviously formed by oxidative cleavage of the N–N bond of the phthalazine moiety.

In contrast, oxidation of **15** employing potassium permanganate (EtOH, H_2O) gave the intensely red pyrimido[4′,5′:4,5]pyrimido[6,1-*a*]phthalazines **17** [e.g. **17a**: M^+ m/z 384 mmu (84%)]. As expected for the zwitterionic ground state of **17**, due to a positive charge centered in the phthalazine unit, the ^1H NMR signal of 9-H was shifted from δ 8.08–8.16 to 8.95–9.02 ppm upon changing from the nonpolar structures **15** to the betaines **17**. Similar to the isoquinoline series, the ^1H NMR signal

of 13-H of compound 17 was observed in the range of δ 8.51–8.78 ppm ($J_{H,H}$ = 8.0–9.0 Hz enlarged), whereas the corresponding resonances of the nonpolar 15 appeared in the region of δ 7.04–7.64 ppm (J could not be determined due to overlap with other signals). Negative solvatochromism was observed [17a: UV-vis (CH_2Cl_2) λ 540, 445, 350, 277 nm; UV-vis (AcOH) λ 500, 385, 312, 263 nm]. Unfortunately, further spectroscopic examinations are prevented by the rather limited solubility of this new class of compounds.

Experimental Section

Methods and Materials. Analyses were carried out by the Mikroanalytisches Laboratorium des Instituts für Organische Chemie und Biochemie, Universität Bonn. Ultraviolet spectra were obtained on a Varian Cary-17 spectrophotometer, and infrared spectra were recorded on a Perkin-Elmer 157-G spectrophotometer. NMR spectra were recorded on either Bruker WH-90, AC-200, or AM-400. The mass spectrometers (MS) used were the A.E.I. (Kratos) MS-30 and MS-50. Melting points are uncorrected. Despite prolonged combustion times and addition of V_2O_5, some compounds failed to give satisfactory elemental analyses due to their extraordinary stability.

MeCN was freshly distilled from P_4O_{10}, 4,4′-bipyridine was freshly sublimed. All other chemicals obtained commercially were used without further purification.

General Procedure for the Preparation of the Zwitterionic Pyridopyrimidopyrimidines (3-8). A stirred suspension of 6-[(triphenylphosphoranylidene)amino]uracil 1 (4.15 g, 10.00 mmol) and the appropriate heteroarene were treated with the isocyanate under argon and refluxed (max temp 130 °C) over the period given below. The excess heteroarene and isocyanate were distilled off *in vacuo*. Unless otherwise noted, the colored residue was then treated with 10–20 mL of ethanol to dissolve the triphenylphosphineoxide. Ethanol-soluble products crystallized on cooling. Molar ratios, purification, and reaction times (in parentheses) are described below.

2,4-Dimethyl-6-(phenylimino)pyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (3a). Phenyl isocyanate (1.43 g, 12.00 mmol) and 30 mL of absolute pyridine were heated at reflux temperature (5 h). The crude product was twice recrystallized from ethanol/dichloromethane to give orange-colored needles: yield 1.37 g (41%); mp 211 °C; IR (KBr) 1700 (CO) cm^{-1}; UV-vis (CH_2Cl_2) λ (log ε) ≈ 565 (2.66), 420 (3.77), 342 (4.18), 281 (4.32), 253 (4.29), 233 (4.32), 225 (4.54), 218 (4.32) nm; ^1H NMR (90 MHz) ($CDCl_3$) δ 3.38 (s, 3, 12-H), 3.45 (s, 3, 13-H), 7.00–7.43 (m, 6, 10-H, ArH), 7.93 (ddd, 1, $^3J_{9,8}$ = 7.9 Hz, $^3J_{9,10}$ = 7.0 Hz, $^4J_{9,11}$ = 2.0 Hz, 9-H), 9.66 (dd, 1, $^3J_{11,10}$ = 8.4 Hz, $^4J_{11,9}$ = 2.0 Hz, 11-H), 9.80 (dd, 1, $^3J_{8,9}$ = 7.9 Hz, $^4J_{8,10}$ = 2.0 Hz, 8-H); ^{13}C NMR (100.26 MHz) ($CDCl_3$, MeOD) δ 28.14 (q, $^1J_{CH}$ = 142.2 Hz, C-12), 29.59 (q, $^1J_{CH}$ = 142.2 Hz, C-13), 85.63 (d, $^3J_{11b-11}$ = 2.4 Hz, C-11b), 118.76 (dddd, $^1J_{CH}$ = 172.8 Hz, $^2J_{9-8}$ = 8.8 Hz, $^3J_{9-11}$ = 3.9 Hz, $^2J_{9-10}$ = 0.5 Hz, C-9), 122.70 (ddd, $^1J_{CH}$ = 177.3 Hz, $^3J_{11-9}$ = 6.3 Hz, $^2J_{11-10}$ = 1.8 Hz, C-11), 123.64 (dtt, $^1J_{CH}$ = 159.3 Hz, $^3J_{17-15}$ = 6.5 Hz, $^2J_{17-16}$ = 2.0 Hz, C-17), 123.86 (ddd, $^1J_{CH}$ = 161.1 Hz, $^3J_{15-17}$ = 7.2 Hz, $^3J_{15-15'}$ = 4.9 Hz, C-15), 128.71 (dd, $^1J_{CH}$ = 158.0 Hz, $^3J_{16-16'}$ = 7.4 Hz, $^2J_{16-17}$ = 1.9 Hz, C-16), 132.86 (ddd, $^1J_{CH}$ = 191.7 Hz, $^3J_{8-10}$ = 8.4 Hz, $^2J_{8-9}$ = 6.0 Hz, overlapped, C-8), 141.26 (dd, $^1J_{CH}$ = 168.3 Hz, $^3J_{10-8}$ = 7.5 Hz, C-10), 144.48 (d, $^3J_{6-8}$ = 2.7 Hz, C-6), 147.42 (m, C-14), 149.05 (m, C-11a), 151.93 (m, C-3), 153.36 (q, $^3J_{4a-13}$ = 2.8 Hz, C-4a), 160.63 (q, $^3J_{1-12}$ = 2.5 Hz, C-1); EIMS (70 eV), *m/z* (rel inten) 333 (M^+; 100); HRMS calcd for $C_{18}H_{15}N_5O_2$ *m/z* 333.1227, found 333.1227. Anal. Calcd for $C_{18}H_{15}N_5O_2$: C, 64.86; H, 4.54; N, 21.01. Found: C, 64.04; H, 4.29; N, 20.90.

6-[(4-Chlorophenyl)imino]-2,4-dimethylpyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3-(2*H*,4*H*)-dione (3b). 4-Chlorophenyl isocyanate (1.84 g, 12.00 mmol) and 30 mL of absolute pyridine were used (5 h). The crude product was first recrystallized from dichloromethane and then from ethyl acetate to give amber-colored crystals: yield 0.95 g (26%); mp 218–220 °C; ^1H NMR (90 MHz) ($CDCl_3$) δ 3.37 (s, 3), 3.44 (s, 3), 7.26–7.28 (m, 5), 7.96 (ddd, 1, *J* = 8.6/7.1/1.4 Hz), 9.62 (dd, 1, *J* = 8.4/1.4 Hz), 9.75 (dd, 1, *J* = 7.9/1.3 Hz).

6-[[(3-Trifluoromethyl)phenyl]imino]-2,4-dimethylpyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (3c). 3-(Trifluoromethyl)phenyl isocyanate (3.00 g, 16.00 mmol) and 15 mL of absolute pyridine were heated for 5 h. The product was recrystallized from ethanol/ethyl acetate to give orange-colored crystals: yield 2.00 g (50%); mp 298 °C; ^1H NMR (200 MHz) ($CDCl_3$) δ 3.41 (s, 3), 3.48 (s, 3), 7.28–7.55 (m, 4), 7.80 (m, 1), 7.99 (ddd, 1, *J* = 8.1/7.9/2.4 Hz), 9.65 (ddd, 1, *J* = 8.1/2.0/0.3 Hz), 9.79 (ddd, 1, *J* = 6.3/2.4/0.3 Hz).

2,4-Dimethyl-6-(isopropylimino)pyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (3e). Isopropyl isocyanate (2.13 g, 0.20 mol) and 30 mL of pyridine were required (12 h). The crude product was twice purified chromatographically on silica gel (1. ethyl acetate; 2. acetone) and then recrystallized from ethyl acetate to produce a lemon-yellow solid: yield 0.60 g (20%); mp 209 °C; ^1H NMR (90 MHz) ($CDCl_3$) δ 3.34 (s, 3), 3.51 (s, 3), 1.13 (d, 6, *J* = 6.6 Hz), 4.18 (m, 1), 7.06 (dd, 1, *J* = 6.9/6.2 Hz), 7.82 (ddd, 1, *J* = 8.5/6.9/2.0 Hz), 9.37–9.60 (m, 2).

6-[(4-Nitrophenyl)imino]-2,4-dimethylpyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3-(2*H*,4*H*)-dione (3f). A volume of 50 mL of absolute pyridine and 4-nitrophenyl isocyanate (1.60 g, 10.00 mmol) were used. After 3 h, the pyridine was distilled off and the residue was repeatedly treated with 30 mL of boiling ethanol. Due to the insolubility of **3f**, further purification failed. The orange solid contained inseparable traces of byproducts: yield 1.85 g (49%); mp 231 °C; ^1H NMR (200 MHz) ($CDCl_3$) δ 3.38 (s, 3), 3.42 (s, 3), 7.34–7.42 (m, 3), 7.99 (ddd, 1, *J* = 8.6/8.5/1.7 Hz), 9.66 (dd, 1, *J* = 8.5/1.7 Hz), 9.74 (dd, 1, *J* = 7.1/1.7 Hz).

6-[[(4-Methylphenyl)sulfonyl]imino]-2,4-dimethylpyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (3g). (4-Methylphenyl)sulfonyl isocyanate (2.36 g, 12.00 mmol) and 40 mL of absolute pyridine were required (5 h). After the solvent had been distilled off *in vacuo*, the residue was recrystallized from ethyl acetate to yield a pale yellow, fluorescent solid: yield 1.23 g (30%); mp 268–269 °C; ^1H NMR (90 MHz) ($CDCl_3$) δ 2.35 (s, 3), 3.38 (s, 3), 3.50 (s, 3), 7.25 (d, 2, *J* = 8.0 Hz), 7.92 (d, 2, *J* = 8.0 Hz), 7.46 (ddd, 1, *J* = 7.8/7.1/1.3 Hz), 8.12 (ddd, 1, *J* = 8.2/7.1/1.4 Hz), 9.71 (dd, 1, *J* = 7.8/1.4 Hz), 9.74 (dd, 1, *J* = 8.2/1.3 Hz).

6-(Allylimino)-1,3-dimethylpyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (3h). Allyl isocyanate (1.66 g, 20.00 mmol) and 30 mL of absolute pyridine were used (4 h). The crude product was recrystallized from ethanol to give orange crystals: yield 1.3 g (44%); mp 154 °C; ^1H NMR (200 MHz) ($CDCl_3$) δ 3.40 (s, 3), 3.57 (s, 3), 4.19 (ddt, 2, *J* = 5.6/1.4/1.4 Hz), 5.12 (ddt, 1, *J* = 10.1/2.2/0.5 Hz), 5.30 (ddt, 1, *J* = 17.3/2.2/0.5 Hz), 6.09 (ddt, 1, *J* = 17.3/10.1/5.6 Hz), 7.19 (ddd, 1, *J* = 7.0/6.3/1.4 Hz), 7.88 (ddd, 1, *J* = 9.5/6.3/2.2 Hz), 9.52 (dd, 1, *J* = 9.5/1.4 Hz), 9.58 (dd, 1, *J* = 7.0/2.2 Hz).

Ethyl 1,2,3,4-Tetrahydro-2,4-dimethyl-1,3-dioxo-6-(phenylimino)pyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-9-carboxylate (4a). Phenyl isocyanate (1.43 g, 12.00 mmol) and 8 mL of ethyl nicotinate were heated for 5 h. The crude product was extracted with ethanol/dichloromethane. After filtration from insoluble residues, the filtrate was concentrated whereupon the product crystallized on cooling. Recrystallization from ethyl acetate/dichloromethane gave orange crystals: yield 1.70 g (42%); mp 191 °C; IR (KBr) 1722 (CO), 1708 (CO) cm^{-1}; UV-vis (CH_2Cl_2) (log ε) 550 (3.11), 384 (4.04), 290 (4.39), 208 (4.76) nm; UV (MeOH) λ (log ε) 530 (2.65), 374 (3.46), 283 (3.89), 218 (3.89) nm; ^1H NMR (200 MHz) ($CDCl_3$) δ 1.45 (t, 3, *J* = 7.0 Hz), 3.40 (s, 3), 3.46 (s, 3), 4.48 (q, 2, *J* = 7.0 Hz), 7.11 (m, 1), 7.30–7.41 (m, 4), 8.36 (dd, 1, *J* = 10.0/2.0 Hz), 9.85 (d, 1, *J* = 10.0 Hz), 10.29 (d, 1, *J* = 2.0 Hz); ^{13}C NMR (22.64 MHz) ($CDCl_3$/DMSO) δ 13.60, 27.23, 28.78, 61.51, 85.46, 120.38, 121.19, 122.96, 123.26, 127.67, 134.59, 138.09, 142.13, 145.53, 149.00, 150.33, 152.56, 158.93, 162.04; EIMS (70 eV), *m/z* (rel inten) 405 (M^+, 100). Anal. Calcd for $C_{21}H_{19}N_5O_4$: C, 62.2; H, 4.7; N, 17.3. Found: C, 62.2; H, 4.9; N, 17.4.

Ethyl 1,2,3,4-Tetrahydro-6-[(4-chlorophenyl)imino]-2,4-dimethyl-1,3-dioxopyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-9-carboxylate (4b). 4-Chlorophenyl isocyanate (1.53 g, 10.00 mmol) and 12 mL of ethyl nicotinate were used (4 h). The crude product, obtained by cooling of the ethanol solution, was collected by filtration and was recrystallized from EtOH/CH_2Cl_2 to afford orange crystals: yield 2.40 g (54%); mp 258 °C; ^1H

NMR ($CDCl_3$) δ 1.38 (t, J = 7.1 Hz, 3H), 3.36 (s, 3H), 3.43 (s, 3H), 4.45 (q, J = 7.1 Hz, 2H), 7.20–7.44 (m, 4H), 8.35 (dd, J = 10.0/2.1 Hz, 1H), 9.59 (d, J = 10.0 Hz), 10.27 (d, J = 2.1 Hz).

Ethyl 1,2,3,4-Tetrahydro-6-[[(3-trifluoromethyl)phenyl]imino]-2,4-dimethyl-1,3-dioxopyrido[1′,2′:3,4]pyrimido-[4,5-*d*]pyrimidine-9-carboxylate (4c). 3-(Trifluoromethyl)-phenyl isocyanate (3.18 g, 17.00 mmol) and 14 mL of ethyl nicotinate were required (3 h reflux). After the excess ester had been distilled off *in vacuo*, the residue was treated with ethyl acetate. After filtration, the solution was distilled to dryness and the crude product was chromatographed (silica gel, EtOAc) to give an orange solid: yield 0.71 g (14%); mp 195 °C; ^{1}H NMR (90 MHz) ($CDCl_3$) δ 1.35 (t, 3, J = 8.1 Hz), 3.31 (s, 3), 3.38 (s, 3), 4.39 (q, 3, J = 8.1 Hz), 7.20–7.46 (m, 3), 7.73 (s, 1), 8.31 (dd, 1, J = 9.6/1.8 Hz), 9.55 (dd, 1, J = 9.6/0.4 Hz), 10.24 (dd, 1, J = 1.8/0.4 Hz).

Ethyl 1,2,3,4-Tetrahydro-6-[(4-methylphenyl)imino]-2,4-dimethyl-1,3-dioxopyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-9-carboxylate (4d). 4-Methylphenyl isocyanate (1.33 g, 10.00 mmol) was used. The crude product was twice recrystallized from ethanol/ethyl acetate to give orange crystals: yield 1.55 g (37%); mp 238–239 °C; ^{1}H NMR (90 MHz) ($CDCl_3$) δ 1.40 (t, 3, J = 7.6 Hz), 2.32 (s, 3), 3.35 (s, 3), 3.44 (s, 3), 4.45 (q, 2, J = 7.6 Hz), 7.06–7.40 (m, 4), 8.31 (dd, 1, J = 10.2/2.0 Hz), 9.51 (dd, 1, J = 10.2/0.5 Hz), 10.25 (dd, 1, J = 2.0/0.5 Hz).

Methyl 1,2,3,4-Tetrahydro-2,4-dimethyl-1,3-dioxo-6-(phenylimino)pyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-10-carboxylate (5a). Isocyanate (10 mL) and phenyl isocyanate (1.76 g, 15.00 mmol) were used. Recrystallization from dichloromethane/ethanol/water (100:20:1) resulted in formation of long red needles: yield 1.10 g (28%); mp 248–249 °C; IR (KBr) 1712 (CO) cm^{-1}; UV-vis (CH_2Cl_2) λ (log ε): 470 (3.62), 350 (4.16), 285 (4.32), 242 (4.42) nm; ^{1}H NMR ($CDCl_3$) (200 MHz) δ 3.43 (s, 3), 3.49 (s, 3), 4.03 (s, 3), 7.04–7.17 (m, 1), 7.31–7.40 (m, 4), 7.70 (dd, 1, J = 8.5/1.7 Hz), 9.77 (dd, 1, J = 1.7/0.3 Hz); ^{13}C NMR (100.62 MHz) ($CDCl_3$) δ 28.17, 29.61, 53.62, 86.60, 116.39, 123.52, 123.65, 124.13, 128.58, 133.06, 140.19, 143.77, 146.83, 149.30, 151.28, 153.36, 160.13, 163.75; EIMS (70 eV), m/z (rel inten) 391 (M$^+$, 100). Anal. Calcd for $C_{20}H_{17}N_5O_4$: C, 61.3; H, 4.4; N, 17.9. Found: C, 61.2; H, 4.7; N, 18.2.

Methyl 1,2,3,4-Tetrahydro-6-[(4-chlorophenyl)imino]-2,4-dimethyl-1,3-dioxopyrido[1′,2′:3,4]pyrimido[4,5-d]pyrimidine-10-carboxylate (5b). 4-Chlorophenyl isocyanate (2.30 g, 15.00 mmol) were used. The crude product was recrystallized from ethanol/dichloromethane to form dark-red crystals: yield 1.65 g (39%); mp 241–243 °C; ^{1}H NMR (90 MHz) ($CDCl_3$) δ 3.37 (s, 3), 3.46 (s, 3), 4.04 (s, 3), 7.17–7.42 (m, 4), 7.71 (d, 1, J = 7.5 Hz), 9.73 (d, 1, J = 7.5 Hz), 10.15 (s, 1).

Methyl 1,2,3,4-Tetrahydro-6-[[(3-trifluormethyl)phenyl]imino]-2,4-dimethyl-1,3-dioxopyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-10-carboxylate (5c). The general procedure with 3-(trifluormethyl)phenyl isocyanate (3.18 g, 17.00 mmol) was applied, and the suspension was heated (90 °C) for 4 h. Recrystallization of the crude product from ethyl acetate gives red crystals: yield 2.40 g (52%); mp 201–202 °C; ^{1}H NMR (200 MHz) ($CDCl_3$) δ 3.43 (s, 3), 3.48 (s, 3), 4.05 (s, 3), 7.27–7.52 (m, 3), 7.73 (dd, 1, J = 7.5/2.1 Hz), 7.79 (s, 1), 9.78 (dd, 1, J = 7.5/0.3 Hz), 10.20 (dd, 1, J = 2.1/0.3 Hz).

10-Acetyl-2,4-dimethyl-6-(phenylimino)pyrido[1′,2′:3,4]-pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (6). 4-Acetylpyridine (15 mL) and phenyl isocyanate (1.66 g, 14.00 mmol) were required. Recrystallization from dichloromethane/ethanol gives dark-red crystals: yield 1.16 g (31%); mp 242–243 °C; IR (KBr) 1695 (C=O); UV-vis (CH_2Cl_2) λ (log ε) 485 (3.42), 350 (3.78), 285 (3.94), 244 (4.06) nm; ^{1}H NMR (90 MHz) ($CDCl_3$) δ 2.77 (s, 3), 3.44 (s, 3), 3.47 (s, 3), 7.00–7.37 (m, 5), 7.65 (dd, 1, J = 8.0/2.0 Hz), 9.75 (dd, 1, J = 8.0/ 0.9 Hz), 10.17 (dd, 1, J = 2.0/0.9 Hz); ^{13}C NMR (50.31 MHz) ($CDCl_3$) δ 26.71, 28.18, 29.65, 86.68, 114.50, 123.33, 123.52, 123.70, 128.59, 133.20, 143.72, 144.60, 146.75, 149.88, 151.23, 153.34, 160.35, 195.49; EIMS (70 eV), m/z (rel inten) 375 (M$^+$, 100). Anal. Calcd for $C_{20}H_{17}N_5O_3$: C, 63.99; H, 4.56; N, 18.66. Found: C, 63.57; H, 4.72; N, 18.32.

2,4,10-Trimethyl-6-(phenylimino)pyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (7). Synthesis was as described. Recrystallization from ethanol gives yellow crystals: yield 1.74 g (59%); mp 277 °C; IR (KBr) 1700 (CO); UV-vis (CH_2Cl_2) λ (log ε) = 548 (2.79), 395 (3.76), 341 (4.13), 286 (4.26), 230 (4.38), 210 (4.69) nm; ^{1}H NMR (90 MHz) ($CDCl_3$) δ 3.38 (s, 3), 3.45 (s, 3), 2.53 (s, 3), 7.31–7.43 (m, 5), 7.11 (d, 1, J = 7.4 Hz), 9.47 (d, 1, J = 0.5 Hz), 9.71 (d, 1, J = 7.4 Hz); ^{13}C NMR (100.62 MHz) ($CDCl_3$/DMSO/TFA) δ 23.01, 29.09, 30.72, 92.20, 122.87, 124.12, 125.55, 128.26, 129.99, 131.69, 137.37, 147.82, 149.30, 151.09, 154.11, 157.74, 160.03 ; EIMS (70 eV), m/z (rel inten) 347 (M$^+$, 100). Anal. Calcd for $C_{19}H_{17}N_5O_2$: C, 65.70; H, 4.93; N, 20.16. Found: C, 64.62; H, 4.04; N, 20.14.

10-[2-(4-Pyridyl)ethyl]-2,4-dimethyl-6-(phenylimino)-pyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (8). 1,2-Di(4-pyridinyl)ethane (2.21 g, 12.00 mmol) and excess phenyl isocyanate were required. The suspension was heated at reflux temperature for 7 h. After the solvent had been distilled off *in vacuo*, the residue was chromatographed on silica gel (EtOAc) to remove byproducts. The crude product was obtained by elution with ethanol and was recrystallized from ethanol/dichloromethane/water (50:30:1) to give yellow crystals: yield 0.30 g (6%); mp 174–176 °C; IR (KBr) 1695 (CO) cm^{-1}; UV-vis (CH_2Cl_2) λ (log ε) 530 (2.96), 410 (3.77), 343 (4.16), 280 (4.24), 255 (4.27; shoulder), 235 (4.42) nm; ^{1}H NMR (200 MHz) ($CDCl_3$) δ 3.42 (s, 3), 3.48 (s, 3), 3.00–3.19 (m, 4), 7.02–7.40 (m, 9), 9.50 (d, 1, J = 1.6 Hz), 9.68 (d, 1, J = 8.5 Hz); EIMS (70 eV), m/z (rel inten) 438 (M$^+$, 100). Anal. Calcd for $C_{25}H_{22}N_6O_2$: C, 68.5; H, 5.0; N, 19.2. Found: C, 68.2; H, 5.4; N, 19.0.

Synthesis of the 10-(4-Pyridinyl)pyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-diones (9). To a stirred suspension of the (uracilylimino)phosphorane 1 (4.15 g, 10.00 mmol) and 4-4′-bipyridine (1.56 g, 10.00 mmol) in 5 mL of MeCN under argon was added the isocyanate [**a**: phenyl, 2.38 g (20.00 mmol); **b**: 4-chlorophenyl, 3.06 g (20.00 mmol); **c**: 3-(trifluoromethyl)phenyl, 3.18 g (17.00 mmol); **d**: 4-methylphenyl, 2.00 g (15.00 mmol)]. After heating for 5 h, the reaction mixture was filtered to afford **9a,b,d**; **9c** was obtained as described below.

2,4-Dimethyl-6-(phenylimino)-10-(4-pyridinyl)pyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (9a). Repeated recrystallization from MeCN gave a pale ruby solid: yield 1.23 g (30%); mp 278 °C; IR (KBr) 1697 (CO) cm^{-1}; UV-vis (CH_2Cl_2) (measured qualitatively because of insufficient solubility) λ 453, 353, 257, 208 nm; ^{1}H NMR (400 MHz) (CD_2Cl_2) δ 3.36 (s, 3), 3.44 (s, 3), 7.050 (tt, 1, J = 7.4/1.3 Hz), 7.323 (dd, J = 8.4/7.4 Hz, 2), 7.395 (dd, J = 8.4/1.3 Hz, 2), 7.510 (dd, J = 6.8/2.0 Hz, 1), 7.686 (dd, J = 6.0/1.8 Hz, 2), 8.786 (dd, J = 6.0/1.6 Hz, 2), 9.800 (dd, J = 6.8/0.8 Hz, 1), 9.965 (dd, J = 2.0/0.8 Hz, 1); ^{13}C NMR (100.62 MHz) (CH_2Cl_2) δ 28.13, 29.62, 86.10, 116.20, 120.24, 121.73, 123.54, 123.97, 128.77, 133.55, 143.34, 144.29, 147.68, 149.28, 149.73, 151.40, 151.58, 153.89, 160.63; EIMS (70 eV), m/z (rel inten) 410 (M$^+$, 100); HRMS calcd for $C_{23}H_{18}N_6O_2$, m/z 410.1492, found 410.1500. Anal. Calcd for $C_{23}H_{18}N_6O_2 \cdot {}^1/_2H_2O$: C, 65.86; H, 4.56; N, 20.04. Found: C, 65.31; H, 4.71; N, 20.15.

6-[(4-Chlorophenyl)imino]-2,4-dimethyl-10-(4-pyridinyl)-pyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (9b). Repeated recrystallization from MeCN gave an orange solid: yield 0.83 g (26%); mp 305–308 °C; HRMS calcd for $C_{23}H_{17}ClN_6O_2$ m/z 444.1101, found 444,1110.

6-[[3-(Trifluoromethyl)phenyl]imino]-2,4-dimethyl-10-(4-pyridinyl)pyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3-(2*H*,4*H*)-dione (9c). After the solvent had been distilled off *in vacuo*, the residue was treated with boiling ethanol; 9c crystallized on cooling overnight and was recrystallized form ethyl acetate to give a red solid: yield 1.45 g (30%); mp 248–249 °C; ^{1}H NMR (200 MHz) ($CDCl_3$) δ 3.44 (s, 3), 3.50 (s, 3), 7.30–7.57 (m, 4), 7.72 (dd, 2, J = 6.2/0.3 Hz), 7.81 (s, 1), 8.85 (d, J = 6.2 Hz, 2), 9.84 (dd, J = 8.4/0.2 Hz, 1), 10.04 (dd, J = 1.5/0.2 Hz, 1).

6-[(4-Methylphenyl)imino]-2,4-dimethyl-10-(4-pyridinyl)-pyrido[1′,2′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (9d). The crude product was extracted twice with dichloromethane/ethanol to give a red, amorphous solid: yield 1.50 g (35%); mp 295–300 °C; ^{1}H NMR (90 MHz) ($CDCl_3$) δ 2.31 (s, 3), 3.38 (s, 3), 3.47 (s, 3), 7.04–7.55 (m, 4), 8.80 (d, 2, J = 6.1 Hz), 7.64 (d, 2, J = 6.1 Hz), 9.80 (d, 1, J = 7.6 Hz), 9.94 (d, 1, J = 2.0 Hz).

(−)-2,4-Dimethyl-6-(phenylimino)-9-(1-methyl-2-pyrrolidinyl)pyrido[1′,2′:3,4]pyrimido-[4,5-*d*]pyrimidine-1,3-(2*H*,4*H*)-dione (10). A solution of 4.15 g (10.00 mmol) of 1, 1.19 g (10.00 mmol) of phenyl isocyanate in 10 mL of (−)-nicotine is heated under argon for 12 h. After remaining nicotine was

distilled off *in vacuo*, the oily residue was chromatographed twice on silica gel [1. EtOAc; 2. EtOH/EtOAc (3:1)] to yield 10 as orange needles: yield 0.25 g (10%); mp 213–217 °C; IR (KBr) 1702 cm^{-1}; UV-vis (CH_2Cl_2) λ (log ε) = 540 (2.60), 418 (3.64), 342 (4.02), 285 (4.08), 232 (4.22); ^1H NMR (200 MHz) ($CDCl_3$) δ 1.62–2.43 (m, 6), 2.21 (s, 3), 3.43 (s, 3), 3.48 (s, 3), 3.28 (t, 1, *J* = 7.5 Hz), 7.02–7.15 (m, 1), 7.30–7.41 (m, 4), 8.09 (dd, 1, *J* = 9.3/3.0 Hz), 9.60 (d, 1, *J* = 9.3 Hz), 9.65 (d, 1, *J* = 3.0 Hz); ^{13}C NMR (22.64 MHz) ($CDCl_3$) δ 22.94, 28.03, 29.42, 34.82, 40.39, 56.87, 67.87, 85.51, 122.99, 123.22, 123.48, 128.56, 130.41, 135.03, 140.57, 144.49, 147.66, 148.27, 151.61, 153.16, 160.35; EIMS (70 eV), *m/z* (rel inten) 416 (M^+, 50), 360 (M^+ – MeNCO, 100); HRMS calcd for $C_{23}H_{24}N_6O_2$: 416.1961, found 416.1975.

(+)-2,4-Dimethyl-6-(phenylimino)-9-[5-(1-methyl-2-oxopyrrolidinyl)]pyrido[1′,2′:3,4]pyrimido[4,5-d]pyrimidine-1,3(2*H*,4*H*)-dione (11). A suspension of the (uracilylimino)phosphorane 1 (2.30 g, 5.50 mmol), (–)-cotinine (1.06 g, 5.70 mmol), and 12 mL of phenyl isocyanate was heated under argon (100 °C) over a period of 5 h. After the reaction mixture had been distilled off *in vacuo*, the oily residue was treated with 20 mL of aqueous ethanol and refluxed for 20 min. After cooling, the crude product was filtered off and chromatographed twice on silica gel (1. ethyl acetate and then ethanol; 2. dichloromethane/ethyl acetate) to give an orange oil which crystallized on cooling as orange prisms: yield 0.43 g (10%); mp 242 °C; ^1H NMR (100.62 MHz) ($CDCl_3$) δ 1.90–1.97 (m, 1), 2.48–2.68 (m, 3), 2.71 (s, 3), 3.40 (s, 3), 3.46 (s, 3), 4.66 (t, *J* = 8.8 Hz, 1), 7.05 (m, 1), 7.33–7.35 (m, 4), 7.76 (d, *J* = 9.7 Hz, 1), 9.65 (d, *J* = 9.7 Hz, 1), 9.70 (d, *J* = 1.7 Hz, 1).

1,2,3,4-Tetrahydro-2,4-dimethyl-1,3-dioxo-6-(phenylimino)-pyrido[1′,2′:3,4]pyrimido[4,5-d]pyrimidinium Hydrochloride (12). The pyridopyrimidopyrimidine **3a** (3.33 g, 10.00 mmol) was dissolved in 50 mL of concd hydrochloric acid, heated for 1 h, and then distilled to dryness to afford a pale yellow solid: yield 3.70 g (100%); mp >180–200 °C dec to give **3a** (mp 211 °C; yield 100%); IR (KBr) 2900–3100 (broad), 1710 (CO) cm^{-1}; ^1H NMR (200 MHz) (DMSO) δ 3.28 (s, 3), 3.32 (s, 3), 7.21 (t, *J* = 7.4 Hz, 1), 7.44 (t, *J* = 7.4/7.4 Hz, 2), 7.58 (d, *J* = 7.4 Hz, 2), 7.81 (dd, *J* = 7.8/6.8 Hz, 1), 8.42 (dd, *J* = 9.0/7.8 Hz, 1), 9.62 (d, *J* = 9.0 Hz, 1), 9.84 (d, *J* = 6.8 Hz, 1); ^{13}C NMR (50.31 MHz) ($CDCl_3$, TFA-d_1) δ 24.96, 26.45, 88.04, 118.11, 119.79, 120.47, 124.20, 125.26, 127.89, 130.61, 139.15, 143.39, 144.59, 146.53, 148.96, 154.98; FABMS, *m/z* (rel inten): 334 (M^+, 100). Anal. Calcd for $C_{18}H_{16}N_5O_2Cl·0.5\ H_2O$: C, 57.1; H, 4.5; N, 18.5. Found: C, 57.3; H, 4.3; N, 18.7.

General Procedure for the Preparation of the Zwitterionic Pyrimidopyrimidoisoquinolines (13). A mixture of (uracilylimino)phosphorane 1 (4.15 g, 10.00 mmol), isocyanate [**a**: phenyl, 1.43 g (12.00 mmol); **b**: 4-chlorophenyl, 1.82 g (12.00 mmol); **c**: 3-trifluoromethyl, 2.80 g (15.00 mmol); **d**: 4-methylphenyl, 2.00 g (15.00 mmol)], and 10 g of isoquinoline was heated over a period of 6 h.

2,4-Dimethyl-6-(phenylimino)pyrimido[4′,5′:4,5]pyrimido-[6,1-a]isoquinoline-1,3(2*H*,4*H*)-dione (13a). After the residual isoquinoline was distilled off *in vacuo*, the dark oil obtained was chromatographed on silica gel (EtOAc) to afford 13a as a reddish orange solid: yield 1.68 g (44%): mp 227–228 °C; ^1H NMR (200 MHz) ($CDCl_3$) δ 3.42 (s, 3), 3.45 (s, 3), 6.95 - 8.00 (m, 9), 8.40 (d, *J* = 7.8 Hz, 1), 9.43 (d, *J* = 7.8 Hz, 1); ^{13}C NMR (100.62 MHz) ($CDCl_3$) δ 28.74, 29.63, 89.20, 117.42, 122.67, 123.30, 123.46, 125.05, 126.16, 126.79, 128.53, 132.64, 134.78, 136.21, 145.07, 147.49, 151.66, 152.22, 154.64, 160.13; EIMS, *m/z* (rel inten) 383 (M^+, 100); HRMS calcd for $C_{22}H_{17}N_5O_2$ *m/z* 383.1382, found 383.1389. Anal. Calcd for $C_{22}H_{17}N_5O_2$: C, 68.92; H, 4.47; N, 18.27. Found: C, 68.31; H, 5.05; N, 18.09.

6-[(4-Chlorophenyl)imino]-2,4-dimethylpyrimido[4′5′:4,5]-pyrimido[6,1-a]isoquinoline-1,3(2*H*,4*H*)-dione (13b). After the isoquinoline had been distilled off *in vacuo*, the residue was treated with ethanol/dichloromethane to dissolve byproduct and residual isoquinoline and then chromatographed on silica gel (ethyl acetate) to give **13b** as an amber solid: yield 0.80 g (19%); mp 275–277 °C; ^1H NMR (400 MHz) (CD_2Cl_2) δ 3.43 (s, 3), 3.47 (s, 3), 7.26–7.33 (m, 4), 7.48 (d, *J* = 7.7/0.7 Hz, 1), 7.59 (t, *J* = 8.7/1.7 Hz, 1), 7.80 (d, *J* = 8.7/1.7 Hz, 1), 7.88 (t, *J* = 8.7/1.2 Hz, 1), 8.37 (d, *J* = 8.7/1.2 Hz, 1), 9.39 (d, *J* = 7.7 Hz, 1).

6-[[(3-Trifluoromethyl)phenyl]imino]-2,4-dimethylpyrimido[4′,5′:4,5]pyrimido[6,1-a]isoquinoline-1,3(2*H*,4*H*)-dione (13c). Column chromatography (silica gel; ethyl acetate/ethanol = 10:1) of the crude product gives 13c as an orange amorphous solid: yield 1.18 g (26%); mp 156 °C; ^1H NMR (90 MHz) ($CDCl_3$) δ 2.74 (s, 3), 2.76 (s, 3), 6.60–8.03 (m, 8), 8.22 (d, *J* = 10.0 Hz, 1), 8.73 (d, *J* = 8.0 Hz, 1).

6-[(4-Methylphenyl)imino]-2,4-dimethylpyrimido[4′,5′:4,5]pyrimido[6,1-a]isoquinoline-1,3(2*H*,4*H*)-dione (13d). After the excess isoquinoline had been distilled off *in vacuo*, the remaining oil was extracted with diethyl ether and then chromatographed (silica gel; ethyl acetate) to form **13d** as a pale red solid: yield 0.71 g (18%); mp 240 °C; ^1H NMR (90 MHz) ($CDCl_3$) δ 2.36 (s, 3), 3.45 (s, 3), 3.51 (s, 3), 6.93–7.77 (m, 8), 8.40 (d, *J* = 8.2 Hz, 1), 9.43 (d, *J* = 7.0 Hz, 1).

General Procedure for the Preparation of the 6-(Arylamino)-1*H*,2*H*-isoquino[2′,1′:3,4]pyrimido[4,5-*d*]pyrimidines 14 and of the 6-(Arylamino)-1*H*,2*H*-phthalazino[2′,1′:3,4]pyrimido[4,5-*d*]pyrimidines 15. A mixture of the iminophosphorane 1 (4.15 g, 10.00 mmol), isocyanate [**a**: phenyl, 1.19 g (10.00 mmol); **b**: 4-chlorophenyl, 2.28 g (15.00 mmol); **c**: 3-(trifluoromethyl)phenyl, 2.80 g (15.00 mmol); **d**: 4-methylphenyl, 1.40 g (15.00 mmol)] and the heteroarene [isoquinoline, 1.29 g (10.00 mmol) in 60 mL of dry MeCN; phthalazine, 1.30 g (10.00 mmol) in 20 mL of dry MeCN] was refluxed under argon until all visible traces of the starting material were replaced by a nearly colorless precipitate, which was collected by filtration. The products were finally obtained by recrystallization from CH_2Cl_2/EtOH (10:1) without heating.

2,4-Dimethyl-6-(phenylamino)-1*H*,2*H*-isoquino[2′,1′:3,4]-pyrimido[4,5-*d*]pyrimidine-1,3-(2*H*,4*H*)-dione (14a). Isolated as colorless solid (3.35 g, 87%): mp 267 °C (oxid); IR (KBr) 3325 (NH), 1680 (CO) cm^{-1}; UV-vis (MeOH) λ (log ε) 350 (3.54), 297 (4.11), 241 (4.07) nm; ^1H NMR (200 MHz) (CD_2Cl_2) δ 3.33 (s, 3), 3.39 (s, 3), 5.58 (s, 1), 6.30 (broad s, 1), 6.71 (d, *J* = 6.6 Hz, 1), 6.86 (d, *J* = 6.6 Hz, 1), 7.00–7.42 (m, 9); ^{13}C NMR (100.62 MHz) (CD_2Cl_2) δ 27.89, 29.76, 55.07, 83.53, 122.35, 122.55, 123.87, 124.65, 125.03, 125.14, 128.02, 128.61, 129.15, 130.89, 133.29, 137.62, 150.24, 152.78, 152.80, 161.89; EIMS (70 eV), *m/z* (rel inten) 385 (M^+, 84), 293 (100). Anal. Calcd for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.96; N, 18.17. Found: C, 68.31; H, 5.05; N, 18.09.

6-[(4-Chlorophenyl)amino]-2,4-dimethyl-1*H*,2*H*-isoquino-[2′,1′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (14b). Amorphous, colorless solid which oxidized on standing: yield 3.81 g (91%); mp 258 °C; ^1H NMR ($CDCl_3$/DMSO) δ 3.24 (s, 3), 3.13 (s, 3), 5.37 (s, 1), 6.51 (d, *J* = 7.6 Hz, 1), 6.80–7.44 (m, 7), 8.71 (broad s, 1).

6-[[-3-(Trifluoromethyl)phenyl]amino]-2,4-dimethyl-1*H*,2*H*-isoquino[2′,1′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3-(2*H*,4*H*)-dione (14c). Colorless solid: yield 6.47 g (70%); mp 265–268 °C; ^1H NMR (90 MHz) ($CDCl_3$) δ 3.43 (s, 3), 3.44 (s, 3), 5.62 (s, 1), 6.55–7.42 (m, 10), 7.88 (s, broad, 1).

6-[(4-Methylphenyl)amino]-2,4-dimethyl-1*H*,2*H*-isoquino-[2′,1′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (14d). Pale yellow solid: yield 2.71 g (68%); mp 266–268 °C; ^1H NMR (90 MHz) ($CDCl_3$) δ 2.14 (s, 3), 3.36 (s, 6), 5.57 (s, 1), 6.43 (s, broad, 1), 6.51–7.33 (m, 10).

2,4-Dimethyl-6-(phenylamino)-1*H*,2*H*-phthalazino[2′,1′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (15a). Pale yellow solid: yield 3.40 g (88%); mp 242–243 °C; IR (KBr) 3345 (NH), 1685 (CO) cm^{-1}; UV-vis (CH_2Cl_2) λ (log ε): 382 (3.48), 314 (4.42), 252 (4.27), 226 (4.37), 202 (4.64) nm; ^1H NMR ($CDCl_3$) (200 MHz) δ 3.44 (s, 3), 3.52 (s, 3), 5.62 (d, *J* = 0.5 Hz, 1), 8.12 (broad, 1), 8.16 (d, *J* = 0.5 Hz, 1), 7.09–7.61 (m, 9); ^{13}C NMR (CD_2Cl_2) (100.62 MHz) δ 27.88, 30.01, 54.23, 84.59, 121.90, 124.76, 124.81, 125.23, 125.33, 128.34, 129.15, 131.79, 132.67, 137.60, 149.09, 150.05, 152.64, 152.85, 161.75; EIMS (70 eV), *m/z* (rel inten) 386 (M^+, 86), 385 (100); HRMS calcd for $C_{21}H_{18}N_6O_2$ *m/z* 386.1491, found 386.1496.

6-[(4-Chlorophenyl)amino]-2,4-dimethyl-1*H*,2*H*-phthalazino[2′,1′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (15b). Amorphous, pale brownish solid: yield 3.45 g (95%); mp >400 °C; ^1H NMR (200 MHz) (CD_2Cl_2) δ 3.35 (s, 3), 3.46 (s, 3), 5.57 (s, 1), 7.18–7.60 (m, 8), 8.15 (s, 1), 8.13 (s, broad, 1).

6-[[-3-(Trifluoromethyl)phenyl]amino]-2,4-dimethyl-1*H*,2*H*-phthalazino[2′,1′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (15c). Pale yellow, amorphous solid: yield

1.8 g (40%); mp 224–228 °C; ^{1}H NMR (200 MHz) ($CDCl_3$) δ 3.43 (s, 3), 3.53 (s, 3), 5.64 (s, 1), 7.19–7.60 (m, 7), 8.12 (two singlets overlapped, 2), 8.25 (s, broad, 1).

6-[(4-Methylphenyl)amino]-2,4-dimethyl-1*H*,2*H*-phthalazino[2′,1′:3,4]pyrimido[4,5-*d*]pyrimidine-1,3(2*H*,4*H*)-dione (15d). Amorphous, pale brownish solid: yield 1.76 g (44%); the color changes >200 °C to grey, melting range 280–320 °C; ^{1}H NMR (90 MHz) ($CDCl_3$) δ 2.28 (s, 3), 3.38 (s, 3), 3.46 (s, 3), 5.57 (s, 1), 7.04–7.64 (m, 8), 8.05 (s, broad, 1), 8.08 (s, 1).

Synthesis of the 2′-Cyanophenyl-Substituted Pyrimido[4,5-*d*]pyrimidines (16). A suspension of the phthalazine 15 [**a**: phenyl, 1.0 g (2.60 mmol); **b**: 4-chlorophenyl, 1.0 g (2.40 mmol); **c**: 3-(trifluoromethyl)phenyl, 1.0 g (2.20 mmol), **d**: 4-methylphenyl, 1.0 g (2.50 mmol)] in 40 mL of nitrobenzene was refluxed for 2 h. After the solvent had been partially evaporated, the nearly insoluble precipitate was collected by filtration and washed with diethyl ether.

2-[5-[(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-7-(phenylamino)pyrimido[4,5-*d*]pyrimidinyl]]benzonitrile (16a). Amorphous, colorless solid: yield 0.83 g (90%); mp 324–325 °C; IR (KBr) 3355 (NH), 2220 (CN), 1704 (CO) cm^{-1}; UV-vis (CH_2Cl_2) λ (log ε) 426 (3.58), 283 (4.30), 245 (4.45), 224 (4.43) nm; ^{1}H NMR ($CDCl_3$) (90 MHz) δ 3.00 (br s, 1), 3.17 (s, 3), 3.60 (s, 3), 6.95–7.82 (m, 9); EIMS (70 eV), *m/z* (rel inten) 384 (M^+, 78), 383 (100); HRMS calcd for $C_{21}H_{16}N_6O_2$ *m/z* 384.1324, found 384.1324. Anal. Calcd for $C_{21}H_{16}N_6O_2$: C, 65.62; H, 4.20; N, 21.86. Found: C, 65.09; H, 4.38; N, 21.35.

2-[5-[7-[(4-Chlorophenyl)amino]-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimido[4,5-*d*]pyrimidinyl]]benzonitrile (16b). Amorphous, insoluble grey solid: yield 0.95 g (95%); mp >400 °C; IR (KBr) 3330 (NH), 2220 (CN), 1605 (CO) cm^{-1}.

2-[5-[7-[[3-(Trifluoromethyl)phenyl]amino]-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimido[4,5-*d*]pyrimidinyl]]benzonitrile (16c). Amorphous, grey solid: yield 0.95 g (95%); mp 226 °C; IR (KBr) 3260 (NH), 2222 (CN), 1720 (CO) cm^{-1}; ^{1}H NMR (90 MHz)($CDCl_3$) δ 3.26 (s, 3), 3.64 (s, 3), 7.33–7.88 (m, 8), 8.20 (s, broad, 1).

2-[5-[1,2,3,4-Tetrahydro-7-[(4-Methylphenyl)amino]-1,3-dimethyl-2,4-dioxopyrimido[4,5-*d*]pyrimidinyl]benzonitrile (16d). Grey solid: yield 0.90 g (90%); mp 361 °C; IR (KBr) 3325 (NH), 2222 (CN), 1700 (CO) cm^{-1}; ^{1}H NMR (400 MHz) (CD_2Cl_2) δ 2.32 (s, 3), 3.26 (s, 3), 3.67 (s, 3), 7.18 (d, *J* = 7.2 Hz, 2), 7.45 (ddd, *J* = 8.0/1.4/0.8 Hz, 1), 7.51 (d, *J* = 7.2 Hz, 2), 7.55 (td, *J* = 8.0/8.0/1.4 Hz, 1), 7.68 (td, *J* = 8.0/8.0/1.4 Hz, 1), 7.60 (s, broad, 1), 7.74 (ddd, *J* = 8.0/1.4/0.8 Hz, 1).

General Procedure for the Synthesis of the Zwitterionic Phthalazines (17). A solution of 0.63 g (4.00 mmol) of potassium permanganate in 40 mL of water was added dropwise to a suspension of **15** [**15a**: 1.54 g (4.00 mmol); **15b**: 1.68 g (4.00 mmol); **15c**: 1.81 g (4.00 mmol); **15d**: 1.60 g (4.00 mmol)] in 40 mL of EtOH. After being stirred for 5 h (**15a,b**: at room temp; **15c,d**: at 65 °C), the precipitate (MnO_2) was filtered off and both mother liquor and precipitate were extracted with CH_2Cl_2. After treatment with Na_2SO_4, the solvent was removed under reduced pressure.

2,4-Dimethyl-6-(phenylimino)pyrimido[4′,5′:4,5]pyrimido[6,1-*a*]phthalazine-1,3(2*H*,4*H*)-dione (17a). Recrystallization from CH_2Cl_2/EtOH afforded red crystals: yield 1.09 g (71%); mp 321–323 °C, >210 °C color changes irreversibly to grey; IR (KBr) 1710 (CO) cm^{-1}; UV-vis (CH_2Cl_2) λ (log ε) 540 (2.99), 445 (3.56), 350 (3.94), 277 (4.28), 243 (4.43), 218 (4.38) nm; ^{1}H NMR (90 MHz) ($CDCl_3$) δ 3.40 (s, 3), 3.42 (s, 3), 6.95-7.44 (m, 5), 7.77–8.05 (m, 3), 8.78 (d, *J* = 8.1 Hz), 9.00 (s, 1); ^{13}C NMR (200 MHz) ($CDCl_3$) δ 28.45, 29.29, 89.53, 122.73, 122.79, 123.92, 126.11, 126.33, 127.99, 131.48, 131.74, 135.45, 146.07, 147.08, 148.00, 150.38, 150.93, 153.34, 159.37; EIMS (70 eV), *m/z* (rel inten) 384 (M^+, 81), 382 (100); HRMS calcd for $C_{21}H_{16}N_6O_2$ *m/z* 384.1332, found 384.1335. Anal. Calcd for $C_{21}H_{16}N_6O_2$: C, 65.62; H, 4.20; N, 21.86. Found: C, 65.37; H, 4.33; N, 21.63.

6-[(4-Chlorophenyl)imino]-2,4-dimethylpyrimido[4′,5′:4,5]pyrimido[6,1-*a*]phthalazine-1,3(2*H*,4*H*)-dione (17b). Recrystallization from dichloromethane/ethanol (30:1) without heating formed purple crystals: yield 0.55 g (33%); mp 399–401 °C, >260 °C color changes to grey; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 3.38 (s, 3), 3.40 (s, 3), 7.08–7.40 (m, 4), 7.77–8.22 (m, 3), 8.60 (d, 1, *J* = 9.0 Hz), 9.02 (s, 1).

6-[[3-(Trifluoromethyl)phenyl]imino]-2,4-dimethylpyrimido[4′,5′:4,5]pyrimidine[6,1-*a*]phthalazine-1,3(2*H*,4*H*)-dione (17c). Recrystallization from dichloromethane (great amounts were required) without heating gave red, nearly insoluble crystals: yield 0.43 g (23%); mp 239 °C; HRMS calcd for $C_{22}H_{15}F_3N_6O_2$ *m/z* 452.1209, found 452.1214.

6-[(4-Methylphenyl)imino]-2,4-dimethylpyrimido[4′,5′:4,5]pyrimido[6,1-a]phthalazine-1,3(2*H*,4*H*)-dione (17d). The crude product was treated with boiling ethanol to give red crystals: yield 1.44 g (90%): mp 364–366 °C, >150 °C color changed irreversibly to grey; ^{1}H NMR (200 MHz) (CD_2Cl_2) δ 3.48 (s, 3), 3.51 (s, 3), 2.32 (s, 3), 7.11–7.18 (m, 4), 7.81–8.09 (m, 3), 8.51 (dd, 1, *J* = 8.0/3.2 Hz), 8.95 (s, 1).

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Supplementary Material Available: Additional compound characterization data (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.