On the Synthesis of Zwitterionic Heteropolycyclic Pyrazoles by a Three-Component Reaction. Some Mechanistic Considerations[1]

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The novel three-component reaction involving a heterocyclic iminophosphorane, an isocyanate, and a hetarene component is applied to an aromatic pyrazole iminophosphorane **1** and to an analogous pyrazolone derivative **13**. The hitherto unknown zwitterionic pyrazolo[3′,4′:4,5]pyrimido[6,1-*a*]-isoquinolines **11a,b** and **16a,b**, pyrazolo[3′,4′:4,5]pyrimido[6,1-*a*]phthalazine **6b**, and pyrazolo[3′,4′:4,5]pyrido[6,1-*a*]pyrimidines **15a,b** are obtained. Additionally, the novel cycloaddition products with triazolinediones, the pyrazolo[3,4-*e*][1,2,4]triazolo[1,2-*a*][1,2,4]triazinediones **9a,b**, are described. The isolation of the dihydro compound **4** and the phthalazinium salt **5** supports a stepwise mechanism for the zwitterion formation. While the influence of the aromaticity of the iminophosphorane component appears to be negligible, the aromaticity of the hetarene component determines the limitations of this versatile reaction. X-ray structures of **11a**, **5b**, and **16b** as well as UV-, MS-, and NMR-spectra and semiempirical calculations confirm the zwitterionic character of the reaction products.

Introduction

Recently, we reported on a novel three-component heteroannulation reaction which converts the iminophosphorane of 6-aminouracil into heterooligocyclic ring systems[3a,b] on treatment with an excess of an aryl isocyanate in the presence of a hetarene. Most probably, this reaction proceeds *via* the initial formation of a carbodiimide from the iminophosphorane and the isocyanate (by an aza-Wittig process) which reacts subsequently with the hetarene to give a [4 + 2]-cycloadduct. The latter one undergoes a final oxidation affording heterocyclic zwitterions.

The conditions and limitations of this reaction are well documented for the heterocyclic substrate 6-aminouracil, but no hetero*aromatic* iminophosphorane species has been examined up to now. While for the uracil substructure in the reaction products a stabilizing effect due to the β-enamino carbonyl chromophore is to be expected (and in fact has been observed[3b]), such considerations cannot be taken into account for aromatic iminophosphoranes. Hence, a different behavior was expected. Furthermore, it was of interest whether the final oxidation step is influenced by the nature of the iminophosphorane component.

It appeared to be advantageous to compare a heteroaromatic iminophosphorane with a nonaromatic analog possessing a β-enamino carbonyl substructure. In order to minimize steric effects, we chose the pyrazole derivatives **1** and **13** for our investigations, which were prepared from the corresponding amines by standard methods.[3i,j] Their reaction with a broad range of different hetarenes and isocyanates promised to enable a versatile access to novel and hitherto unknown tri- and tetracyclic ring systems with interesting steric and electronic properties. Besides, polyheterocyclic compounds are known to possess various biological activities and the resulting fused pyrazoles are of interest as potential bioactive lead substances[4] or dyes.

Results and Discussion

Reactions of the Pyrazole Derivative 1. The pyrazole iminophosphorane **1** reacts with various isocyanates and hetarenes in a three-component reaction as described for 6-aminouracil,[3a–c] affording the heteroannulated pyrazoles **6b** and **11a,b** as the final products (Scheme 1 and 2).[5a] Usually, acetonitrile is used as a solvent; a 3-fold excess of the hetarene component is added together with 3–10 equiv of the isocyanate to the suspension of the iminophosphorane. After addition of the components, the resulting mixture is heated to gentle reflux for ca 3 h. The progress of the reaction can be easily monitored: At the beginning the clear solution turns light yellow upon warming. Above 60 °C the color of the solution becomes increasingly intensive (red, orange, or yellow), indicating the formation of the zwitterions.

The most interesting and detailed investigations were conducted with phthalazine **3** as the hetarene component (Scheme 1). Here, as long as an 2-fold excess of the isocyanate is employed, two products are obtained in the reaction: On cooling of the reaction mixture to room temperature a solid precipitates which was identified as the dihydrotetracycle **4**. The removal of the solvent

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(1) Part 4 of our series: Three-component cyclizations with heterocyclic iminophosphoranes; Part 3 see ref 3b.

(2) Taken in part from the Ph.D. thesis of C. Bamberg, Universität Bonn, 1992–1994.

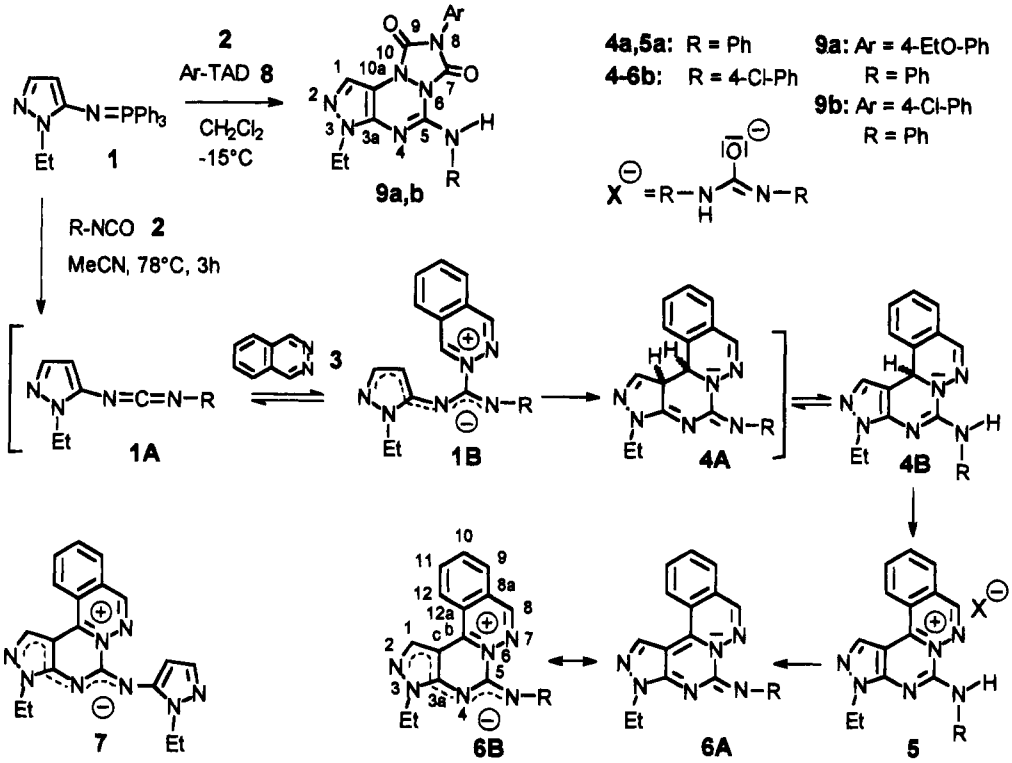
(3) (a) Wamhoff, H.; Schmidt, A.; Nieger, M. *Tetrahedron Lett.* **1991**, 4373. (b) Wamhoff, H.; Schmidt, A. *J. Org. Chem.* **1993**, *58*, 6976. (c) Wamhoff, H.; Schmidt, A. *Heterocycles* **1993**, *35*, 1055. (d) Kosower, E. M. *J. Am. Chem. Soc.* **1958**, *80*, 3253. (e) Kosower, E. M.; Ramsey, B. G. *J. Am. Chem. Soc.* **1959**, *81*, 856. (f) Reichardt, C. *Angew. Chem.* **1979**, *91*, 119. (g) Reichardt, C.; Müller, R. *Liebigs Ann. Chem.* **1976**, *11*, 125 and literature cited therein. (h) Liptay, W. *Angew. Chem.* **1969**, *61*, 195. (i) Wamhoff, H.; Schupp, W.; Kirfel, A.; Will, G. *J. Org. Chem.* **1986**, *51*, 149. (j) Wamhoff, H.; Schupp, W. *J. Org. Chem.* **1986**, *51*, 2787.

(4) (a) Katritzky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, 1984; Vol. 5, p 343, and references cited therein.

(5) (a) Only few representative compounds obtained are described in this paper. The reaction appears to be of quite general applicability. (b) Further details regarding this unexpected reaction are currently under investigation and will be published elsewhere.

0022-3263/94/1959-3985$04.50/0

Scheme 1

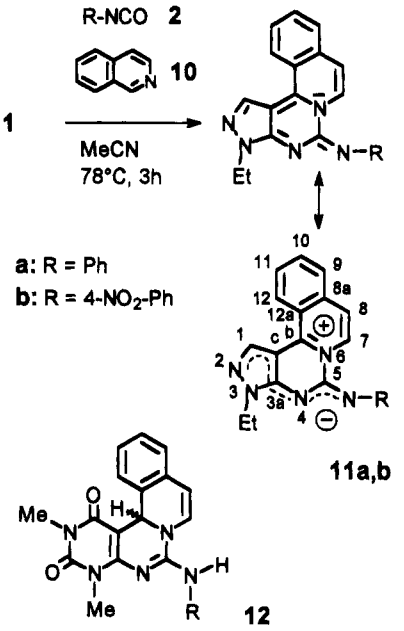


affords an oily residue, which is triturated with warm ethanol. From the solution thus obtained, additional **4** crystallizes together with diarylurea which is the main byproduct. On further concentration, the monohydrohetarenium ureate **5** is obtained from the ethanolic filtrate.

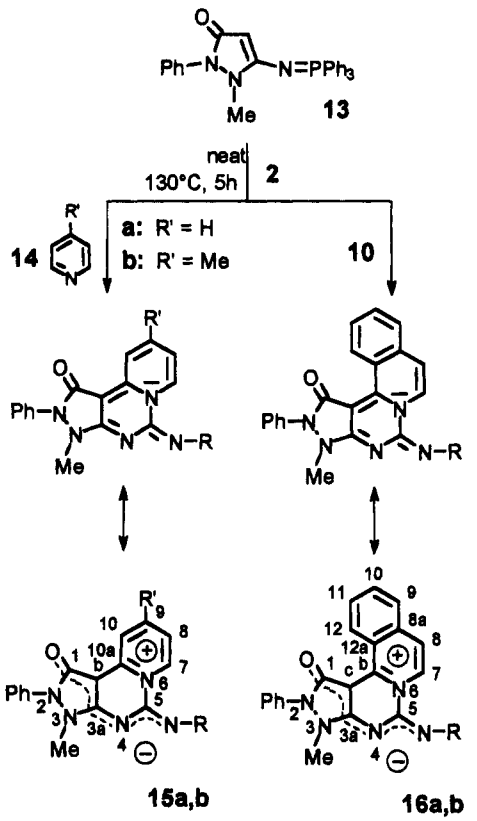
If less than 2 equiv of the isocyanate are present in the reaction mixture, the dihydro compound **4** becomes the main product together with traces of the pyrazolyl-substituted derivative **7** resulting from a formal substitution of the aniline moiety by a second pyrazole amine.[5b] The dihydrotetracycle **4** can be oxidized with $KMnO_4$ to give the zwitterion **6**. This is well generated from the monohydro salt **5** on treatment with a base such as NaOH or NaH. Unexpectedly, *no* reaction is observed employing pyridine and substituted pyridines like γ-picoline. Similarly, isoquinoline **10** as the hetarene component gives good results: after chromatographic purification the zwitterions **11a,b** are obtained in pure isoquinoline or in acetonitrile in ca. 40% yield. In this case no detectable amounts of any di- or monohydro intermediates are formed which were isolated from acetonitrile for the uracil derivative **12** (Scheme 2).[3b] The zwitterions are easily identified by their color and their impressive negative solvatochromism (*vide infra*). Additionally, the ^{1}H–NMR signals of the hetarene part of **6** and **11** show a significant downfield shift of about 1.6–2 ppm. The structures of the monohydro compound **5b** and the zwitterion **11a** are confirmed by X-ray diffraction analysis.

The three differently hydrogenated derivatives **4**–**6** demonstrate the alterations in their electronic systems with their ^{1}H-NMR shifts. For the dihydro compound **4b** the signal of the angular proton H-12b is found at 5.75 ppm and the H-1 signal at 8.2 ppm. While the H-12 signal cannot be unambiguously identified (between 7.45 and 7.65 ppm), the H-8 signal appears at 7.70 ppm (the signal assignments are based on H,H-COSY experiments). In the monohydro salt **5b** the phthalazine moiety has rearomatized and is positively charged. Consequently, all phthalazine signals show a significant downfield shift of about 1–1.3 ppm. The H-8 signal with 9.9 ppm and the H-12 signal with 8.65 ppm indicate the positive charge. The downfield shift of H-1 (found at 9.5 ppm) suggests that this proton is in the vicinity of the positively charged aromatic ring. As can be expected, no H-12b signal is found. The NH signal shifts to 11.4 ppm (from 9.15 ppm) and is significantly broadened due to the inability of the phthalazine N-7 atom to enable a hydrogen bond, while in **4b** the NH signal is very sharp corresponding to a limited exchangeability of the proton. In the zwitterion **6b**, the negative charge of the pyrazole part decreases the shifts due to its anisotropic effect. H-1

Scheme 2



Scheme 3



a: R = 4-Cl-Ph, R' = H

b. R = 4-Cl-3-EtO-Ph, R' = Me

appears at 8.8 ppm (a decrease of 0.7 ppm), H-8 at 9.3 ppm, and H-12 at 8.25 ppm. The altered substituent effect of the tetracycle is reflected in the two signal groups of the 4-chlorophenyl moiety; its AA'BB' signal pattern is shifted upfield for about 0.4 ppm in comparison with the monohydro salt.

Reactions of the Nonaromatic Pyrazole 13. Despite its nonaromaticity,[6] the pyrazolone iminophosphorane **13** shows a behavior analogous to **1** and is converted into the zwitterions **15** and **16** by the same procedure (Scheme 3). In contrast to the pyrazole **1**, the pyrazolone **13** undergoes a three-component reaction[7a] as well with pyridine and pyridine derivatives. Thus, treatment of the carbodiimide generated *in situ* from **13** and aryl isocyanate **2** with pyridine **14a** or γ-picoline **14b** leads to the formation of the zwitterions **15a,b**. In accordance with the suggested mechanism is the observation that ethyl nicotinate as the hetarene gives only low yields of the zwitterion independent from the presence or absence of a solvent. For the pyrazolones, too, isoquinoline **10** appears to be the first-rate hetarene as it gave the best results in the cyclization reaction. The resulting zwitterions **16a,b** show a typical negative solvatochromism[3d-h] comparable to that of the uracil derivatives.[3b]

Obviously, the aromaticity of the iminophosphorane component is of low significance for the feasibility of this reaction. Both the pyrazole derivative and its nonaromatic pyrazolone analog can be converted into zwitterions with comparable yields. On the other hand, the aromaticity of the hetarene component seems to influence the course of the reaction.

Mechanism. Our experimental results lead to the following mechanism (see Scheme 1) which agrees well with that proposed by Wamhoff and Schmidt:[3b] In the first step, the iminophosphorane (e.g. **1**) undergoes an aza-Wittig reaction with the isocyanate component **2** yielding a carbodiimide **1A**. Next, the hetarene component (here **3**) attacks at the electrophilic carbodiimide carbon atom to give the intermediate **1B** in a reversible step. The resulting ylide **1B** is converted into the dihydro intermediate **4** *via* an intramolecular substitution reaction. Oxidation of **4** gives the final product **6**. Although it is possible to represent our novel heterocyclic systems by several Lewis structures, only one uncharged cross-conjugated form can be written, which is obviously disfavored: in formula **6A** for instance, both the pyrazole and the pyridazine part have lost their aromaticity.

For the pyrazole derivatives, the aforementioned mechanism was supported by various observations. Firstly, the carbodiimides could be intercepted by the strong dienophile 4-aryl-triazolinedione (4-Ar-TAD, **8**) yielding the novel tricyclic pyrazolo[3,4-*e*][1,2,4]triazolo[1,2-*a*][1,2,4]-triazines **9a,b** (Scheme 1) as a result of a cycloaddition reaction of the 2-azadiene moiety present in the carbodiimides.[7b] Secondly, as no ^{13}C-NMR experiments were obtainable with the carbodiimides due to their transient nature, we carried out some semiempirical calculations on them. We chose the AM1 method by Dewar et al.[8] for this purpose because it was shown that this method is sufficiently suited to reproduce the geometries of most heterocyclic systems[9] and because we did not intend to calculate transition states. The calculated electrostatic potential[10] is strongly positive around the carbodiimide carbon center. Thus, a nucleophilic attack by a heteroatom of an arene seems to be favored. Furthermore, the orbital coefficients indicate the absence of any isolated diene system capable of a pericyclic reaction. The resulting ylide **1B** is stabilized by conjugation. The subsequent cyclization step was of special interest. While it is possible to consider the ring closure as a 1,6-dipolar cyclization,[3b] this is not likely for delocalized systems as the pyrazoles (with a calculated Bird-aromaticity index[11] of $I_5 = 69.8$, *vide infra*). Thus, we regard this cyclization as an intramolecular substitution reaction, yielding a dihydro product comparable to **4A**. As was observed by van der Plas et al.[12] for extremely electron-deficient heteroaromates, nucleophilic substitution reactions on

(6) (a) The NMR spectra (^{1}H and ^{13}C) of **13** in polar DMSO clearly show the presence of a nonaromatic proton (3.4 ppm) attached to a sp^2-carbon. (b) Katritzky, A. R.; Karelson, M.; Harris, P. A. *Heterocycles* **1991**, *32*, 329. (c) Wiley, R. H; Wiley, . *Pyrazolones, Pyrazolidinones and Derivatives*. In Weissberger, A. *The Chemistry of Heterocyclic Compounds*; Interscience Publishers: New York, 1964; Vol. 20, p 12.

(7) (a) Under the usual conditions, the reaction of a 1:3:3 mixture of **13**, *p*-chlorophenyl isocyanate and *phthalazine* afforded a compound which is most probably the monohydro derivative. Unfortunately, it was impossible to characterize the compound completely up to now. (b) An X-ray structure analysis of **9a** has been carried out. An ORTEP diagram is shown in Figure 6.

(8) (a) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F. *J. Am. Chem. Soc.* **1985**, *107*, 3902. (b) Dewar, M. J. S.; Holder, A. J. *Heterocycles* **1989**, *28*, 1135.

(9) (a) Katritzky, A. R.; Szafran, M.; Malhotra, N.; Chaudry, S. U.; Anders, E. *Tetrahedron Comput. Meth.* **1990**, *5*, 247. (b) Katritzky, A. R.; Barczynski, P.; Musumarra, G.; Pisano, D.; Szafran, M. *J. Am. Chem. Soc.* **1989**, *111*, 7.

(10) Hyperchem release 3.0 (Autodesk Inc.) on a PC with 16 MB RAM, convergence gradient 0.1.

(11) (a) Bird, C. W. *Tetrahedron* **1985**, *41*, 1409. (b) Bird, C. W. *Tetrahedron* **1986**, *42*, 89.

(12) (a) Van der Plas, H. C.; Chupakhin, O. N.; Charushin, V. N. *Tetrahedron* **1988**, *44*, 1. (b) Van der Plas, H. C. *J. Heterocyclic Chem.* **1988**, *25*, 831.

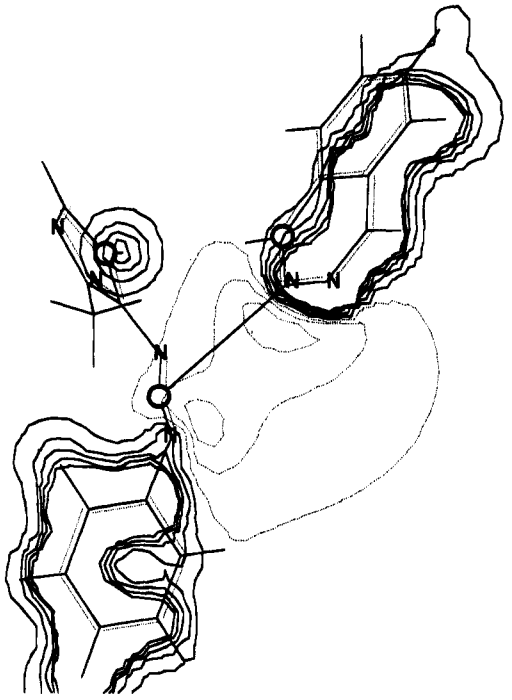


Figure 1. Electrostatic potential 160 pm above the plane marked by the three circles. Continuous lines: positive potential; dashed lines: negative potential; −0.2 to 0.2 au.

such hetarenes can lead to the formation of sometimes isolable σ-adducts which have to be oxidized with $KMnO_4$ to yield the desired products. The hetarenium moiety present in the ylide **1B** can certainly be considered as being extremely electron-deficient. On the other hand, the 4-position of pyrazoles is known to be nucleophilic.[13] This nucleophilicity is enhanced by the conjugation with the negative part of the ylide in **1B**. The calculated electrostatic potential (AM1) for such an ylide is presented in Figure 1.

The potential diagram reveals that a substitution reaction is well possible. The tautomerism, forming a 1,4-dihydro product **4B**, reconstitutes aromaticity in the pyrazole ring. Interestingly, both the pyrazole as well as the pyrazolone derivative undergo oxidation under appropriate conditions so that the zwitterions **11**, **15**, and **16** can be isolated. This "oxidation" step represents further evidence for an intramolecular substitution reaction. Van der Plas et al.[12] have pointed out that the substitution of an aromatic *H-atom* is facilitated if the electron deficiency is enhanced. In this case, a hydride ion is formally superseded. Thus, the "oxidation" has to be considered as a two-step process involving formal hydride and proton displacements. That this is indeed the case in the formation of the pyrazole zwitterions was impressively demonstrated by the isolation and X-ray structure determination of the tetracyclic arenium ion **5b**.[14] Here, the hydride is already displaced, while the proton at the amine position is still present. Besides, the X-ray single-crystal structure of **5b** (Figure 2) unambiguously proves the tautomeric shift of one H-atom

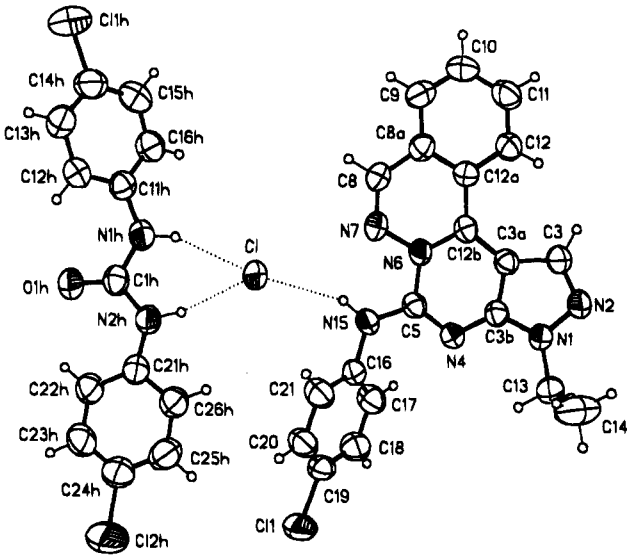


Figure 2. ORTEP diagram of the X-ray structure of **5b**. 50% thermal ellipsoids, one of the two independent molecules.

of the primary substitution product **4A** to this amine position.

The "hydride" is probably accepted by one molecule of the isocyanate (present in excess) which reacts with a second isocyanate molecule to form the counterion of the monohydro salt **5**. This is indicated by ^1H NMR signals similar to those of the corresponding diarylurea with an NH signal referring to only *one* proton. Besides, the unavoidable generation of the diarylurea even in solvents as toluene is thus explained.

A mass spectroscopic examination of **5b** revealed the presence of this diarylurea. From the same sample, a zwitterion mass spectrum was obtained after prolonged measurement at 180 °C. As is seen in the ^1H NMR spectra, the urea and compound **5b** are both present in a chromatographically pure sample.

While the formation of the primary addition product, as an equilibrium, depends on the basicity of the hetarene component, the subsequent intramolecular substitution is dependent on the electron deficiency, which is opposite to the basicity. Hence, the inertness of pyridine and γ-picoline (and DMAP) toward the pyrazole derivative in this three-component reaction is easily explained. While the primary addition products are readily formed, yielding an open-chain ylide, intramolecular substitution does not occur. Van der Plas et al.[12] concluded, that the addition step of the intramolecular substitution occurs more readily with hetarenes of low aromaticity while the hydride abstraction is facilitated by a higher aromaticity of the reconstituted arene. Thus, it can be expected, that pyridines *do* form the primary adduct but do *not* undergo the addition of the pyrazole C-4 atom, whose nucleophilicity is limited due to its aromatic conjugation. On the other hand, the pyrazolone iminophosphorane **13**, as well as the (uracil-6-ylimino)phosphorane, do react with pyridine due to the greater nucleophilicity of their C-4 and C-5 positions, respectively. This is also in accordance with the observation of Wamhoff and Schmidt in their cross-experiments with differently substituted pyridines.[3b]

Besides other methods,[15] the influence of the aromaticity of the participating species can be estimated by

(13) (a) Burton, R. E.; Finar, I. L. *J. Chem. Soc. (B)* **1970**, 1692. (b) Simay, A.; Takács, K.; Horváth, K.; Dvortsák, P. *Acta Chim. Acad. Sci. Hung.* **1980**, *105*, 127. (c) Dorn, H. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1980**, *16*, 1.

(14) The origin of the chloride anion detected in the X-ray structure of **5b** is not sufficiently explained. The only possible chloride sources were the chlorophenyl substituents and the solvent component $CDCl_3$.

(15) Simkin, B. Y.; Minkin, V. I.; Glukhovtsev, M. N. *Adv. Heterocycl. Chem.* **1993**, *56*, 304.

Bird's aromaticity index I_n. It represents the variation of the bond orders in a given cyclic system (which meets the qualitative criteria of aromaticity) and is normalized to be $I = 100$ for a completely delocalized system (benzene). For a totally localized structure, $I = 0$ is obtained. As was shown by Katritzky et al.,[9b] this index can successfully be applied to all heteroaromates, in which the number of heteroatoms does not exceed that of the carbon atoms. However, highly symmetrical structures cannot correctly be estimated.[14]

In our case, the application of Bird's index shows, that in the zwitterion **11** the isoquinolinium ring has an index of $I_{6,6} = 57.3$, and in **5** for the phthalazinium ring $I_{6,6} = 65.2$. (The index $I_{6,6}$ referring to a bicyclic 6,6-ring arene was chosen because the X-ray structures imply two separated aromatic systems in the zwitterions, *vide infra*). For the 10-membered, bicyclic heteroarenes, the calculated (AM1) bond lengths lead to slightly higher aromaticity indices. Still, the value for pyridinium with $I_6 = 74.4$ is the highest,[16] proving that here the temporary suspension of aromaticity is most unfavorable. On the other hand, the reaction with isoquinoline preserves the aromaticity in the benzo part of the bicyclic isoquinoline structure and its aromaticity rises to a value of $I_6 = 83.4$. It can thus be concluded that despite the steric demands in tetracyclic systems such as **6** or **11**, the reaction of bicyclic arene components, e.g. phthalazine or isoquinoline, is favored due to the fact that the aromaticity of the species is never totally suspended.

Once the σ-complex is formed the H-shift *after* the formation allows rearomatization. Hence, it can be expected, that the equilibrium of these two steps, addition and tautomerism, is shifted to the right side of the equation due to the aromatic stabilization of the iminophosphorane component. The hydride elimination following, now regains the aromaticity of the hetarene component (in the case of the bicylic hetarenes for the N-containing ring system).

Structural Features. The three-component reaction of the pyrazole derivatives **1** and **13** with heteroaromatic bicyclic compounds such as isoquinoline leads to the formation of tetracyclic ring systems in which the substituents at the 1- and 12-positions are in relatively close positions. Consequently, we investigated the possibility of helical zwitterions. The calculated structures indicated the generation of helical products with torsion angles of about 17° between the positions 12 and 12c. To verify this hypothesis we carried out the measurement of a NOE-difference spectrum on compound **11a**. Although only qualitatively, a nuclear Overhauser amplification of about 23% made a greater distance between the two protons at the positions 1 and 12 unlikely. The X-ray single crystal structure (Figure 3) of the zwitterion **16b** confirmed this conclusion: the observed torsion angle between C-12 and C-12c amounts to only 4.2° which means an almost total planarity of the tetracyclic system. To achieve this planarity, the zwitterionic system **16b** is distorted at the C12a–C12b bond, the length being 144.4(5) pm and shortened at the C7–C8 bond to only 132.7(5) pm. These bond lengths are at the outer margins for the values possible in aromatic systems.[9b] Interestingly, the aryl substituent seems to be separated from the zwitterion's negative partial charge (despite their conjugation). While the C5–N20 bond possesses the bond order of a double bond (with a length of 129.3(4) pm), the N20–C21 bond has an increased σ-character (length: 140.1(4) pm). Furthermore, the ^{13}C-NMR shifts of the *N*-aryl substituent show almost no differences compared to uncharged anilines. Additionally, the single crystal X-ray analysis documents the charge separation between the isoquinolinium unit and the negative part in the zwitterion: the increased length of the C5–N6 bond (147.5(4) pm (corresponding to a single bond)) leads to the conclusion that there is no π-interaction between the isoquinolinium unit and C5. On the other hand the system is stabilized by the C12b–C12c bond with 141.7(5) pm which has some π-contributions. The corresponding bond lengths obtained for the analogous pyrazole zwitterion from the single crystal X-ray analysis of **11a** (Figure 4) are as follows: C5–N6 147.9(2) pm, C12b–C12c 139.9(2) pm, C12a–C12b 145.1(2) pm, and C7–C8 133.2(3) pm. A further information is provided by the evaluation of the bond lengths: no particular bond length alternance pointing to a localized cross-conjugated structure is observed, supporting the conclusion that two seperate aromatic subsystems form the zwitterionic compounds.

Although the AM1-optimized structure of **11a** differs slightly from the one determined experimentally, the charge separation is well documented by the calculated electrostatic potential (Figure 5). The tetracyclic ring

(16) Pyridinium *N*-oxide. Taken from ref 8b.

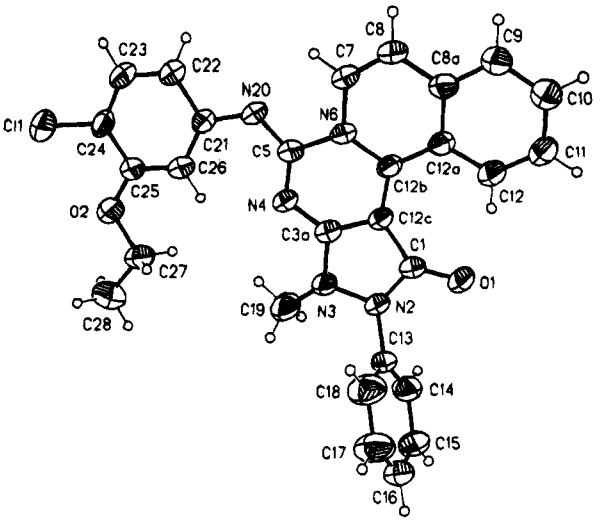


Figure 3. ORTEP diagram of the X-ray structure of **16b**. 50% thermal ellipsoids.

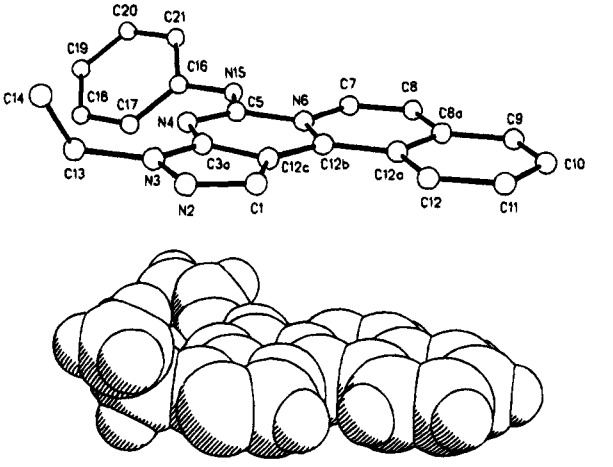


Figure 4. X-ray structure of **11a**. A view from the side demonstrates the planarity of the tetracyclic system.

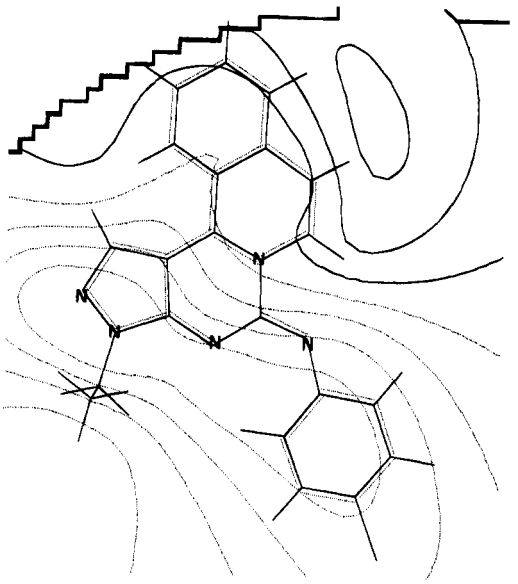


Figure 5. Electrostatic potential 300 pm above the plane of the tetracyclic system. Continuous lines: positive potential; dashed lines: negative potential; −0.02 to 0.02 au.

system appears to be quite rigid. This rigidity is reflected in the IR-spectra of the zwitterions which contain a relatively small number of bands. Additionally, in the MS only a small number of peaks are observed at masses below the molecular mass due to the stability of the polycyclic ring system.

All zwitterions exhibit a pronounced negative solvatochromic effect. For the pyrazolone **15a**, for instance, λ_{max} of the VIS-absorption is shifted from 407 nm in polar 2,2,2-trifluoroethanol to 441 nm in CCl_4. The enhanced delocalization of the negative charge in the zwitterion **11a** prepared from the *aromatic* pyrazole iminophosphorane is impressively demonstrated by its $\Delta\lambda_{max}$ of 120 nm between trifluoroethanol and CCl_4. This shift exceeds by far the effect found for the uracil analogs.[3b]

X-ray Crystallographic Studies of 5b, 9a, 11a, and 16b.[17] All X-ray data were collected at room temperature. The structures were solved by direct methods (SHELXTL-Plus). All non-hydrogen atoms were refined anisotropically, H atoms were refined by using a riding model, and H(N) were refined free (SHELXTL-Plus for **9a**; SHELXL-93 for **5b**, **11a**, and **16b**). An extinction correction was applied on **9a**, **11a**, and **16b**, and an absorption correction on the basis of ψ scans on **11a** and **16b**, respectively. Programs: G.M. Sheldrick, SHELXTL-Plus, Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, 1989. G.M. Sheldrick, SHELXL-93, Univ. of Göttingen, FRG, 1993.

Experimental Section

Methods and Materials. Analyses were carried out by the Mikroanalytisches Laboratorium des Instituts für Organische Chemie und Biochemie, Universität Bonn. NMR spectra were recorded on either Bruker WH-90, WH-200, or WM-250 instruments. The mass spectrometers (MS) used were the A.E.I. (Kratos) MS-30 and MS-50. Despite prolonged combustion times, some compounds failed to give satisfactory elemental analyses due to their extraordinary stability. Infrared spectra were obtained on a Perkin-Elmer 157-G spectrophotometer, and UV spectra were recorded on a Beckman DU-640 spectrophotometer. Melting points are uncorrected. All solvents and liquid reagents (MeCN and hetarenes) were distilled prior to use and dried as usual. All other commercially available chemicals were used without further purification. The synthesis of the 5-amino-1,2-dihydro-1-methyl-2-phenylpyrazol-3-one was accomplished as previously reported,[18,19] while the 5-amino-1-ethylpyrazole was purchased from the Aldrich Chemical Co. Light petroleum ether (bp 40–60 °C) was used whenever this solvent was required. The reactions were carried out in predried glassware under an argon atmosphere. For chromatographic separations, Merck silica gel 60 (70–230 mesh) was used.

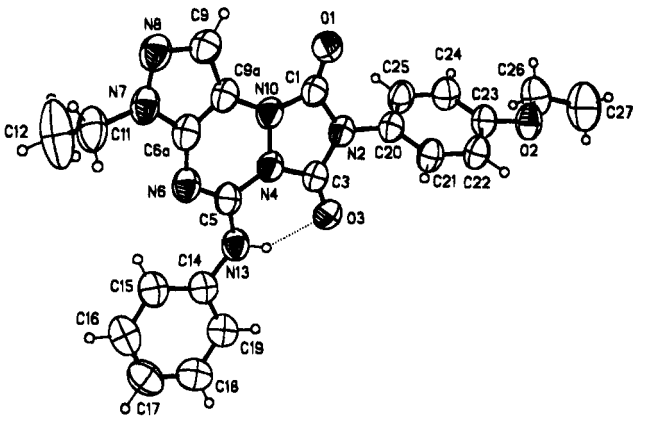


Figure 6. ORTEP diagram of the X-ray structure of **9a**. 50% thermal ellipsoids.

Preparation of the Iminophosphoranes 1 and 13. To a suspension of the aminopyrazole in 75 mL of dry toluene were added PPh_3, C_2Cl_6, and NEt_3 in the molar ratios given below and heated to reflux for 3 h. The hot pale-yellow solution was separated from the precipitated NEt_3·HCl and the solvent was distilled off *in vacuo* to afford a crude solid which was recrystallized from ethanol.

5-[(Triphenylphosphoranylidene)amino]-1-ethylpyrazole (1). An amount of 5 g (40 mmol) of the aminopyrazole, 14.15 g (54 mmol) of PPh_3, and 8.5 g (40 mmol) of C_2Cl_6 were heated together with 12 mL (80 mmol) of NEt_3 to yield 9.8 g (66%) of **1**: mp 111–112 °C; IR (KBr) 3040, 2975, 2925, 1430 cm^{-1}; UV-vis (1,4-dioxane) λ (log ϵ) 242 (3.46) nm; ^1H NMR (90 MHz) ($CDCl_3$) δ 1.4 (t, 3, J = 7.2 Hz), 3.1 (q, 2, J = 7.2 Hz), 7.25 (d, 1, J = 2.1 Hz), 7.3–7.7 (m, 16); ^{13}C NMR (50 MHz) ($CDCl_3$) δ 14.84, 45.64, 90.79 (d, $^3J_{PC}$ = 8.7 Hz, C-4), 128.48 (d, $^3J_{PC}$ = 12.8 Hz, C-12), 129.43 (d, $^1J_{PC}$ = 108.3 Hz, C-10), 131.93 (d, $^2J_{PC}$ = 9.6 Hz, C-11), 132.16 (d, $^4J_{PC}$ = 3.2 Hz, C-13), 133.42 (d, $^4J_{PC}$ = 2.5 Hz, C-3), 137.38 (d, $^2J_{PC}$ = 21.2 Hz, C-5); EIMS (70 eV), *m/z* (rel inten) 371 (M^+, 100). Anal. Calcd for $C_{23}H_{22}N_3P$: C, 74.38; H, 5.97; N, 11.31. Found: C, 74.25; H, 6.00; N, 11.05.

5-[(Triphenylphosphoranylidene)amino]-1,2-dihydro-1-methyl-2-phenylpyrazol-3-one (13). An amount of 10 g (36 mmol) of the aminopyrazolone, 14.15 g (54 mmol) of PPh_3, 8.4 g (36 mmol) of C_2Cl_6, and 10 mL (72 mmol) of NEt_3 were used: yield 13.4 g (83%); mp 209 °C; IR (KBr) 3045, 1650, 1590, 1575, 1430 cm^{-1}; UV-vis (1,4-dioxane) λ (log ϵ) 264 (2.84) nm; ^1H NMR (250 MHz) ($CDCl_3$) δ 4.25 (s, 3), 7.1 (t, 1), 7.3 (t, 2), 7.4–7.6 (m, 13), 7.6–7.75 (m, 5); ^{13}C NMR (60.25 MHz) ($CDCl_3$) δ 36.14, 81.08, 122.49, 124.27, 127.11, 128.61, 128.74, 128.93, 129.13, 132.35, 132.52, 132.68, 132.75, 132.79, 138.20, 166.91, 167.10, 169.43; EIMS (70 eV), *m/z* (rel inten) 449 (M^+, 100); HRMS calcd for $C_{28}H_{24}N_3OP$ *m/z* 449.1657, found 449.1657. Anal. Calcd for $C_{28}H_{24}N_3OP$: C, 74.82; H, 5.38; N, 9.35. Found: C, 74.51; H, 5.41; N, 9.32.

General Procedure for the Preparation of the Pyrazolo[3′,4′:4,5]pyrimido[6,1-*a*] isoquinolinium Betaines,

(17) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

(18) De Graef, H.; Ledrut, J., Combes, G. *Bull. Soc. Chim. Belg.* **1952**, *61*, 331.

(19) Ito, I. *J. Pharm. Soc. Jpn.* **1956**, *76*, 820.

Table 1. Crystallographic Data and Summary of Data Collection and Refinement[a]

	5b	9a	11a	16b
formula	$C_{33}H_{26}Cl_4N_8O$	$C_{22}H_{21}N_7O_3$	$C_{21}H_{17}N_5$	$C_{28}H_{22}ClN_5O_2$
cryst syst	triclinic	triclinic	monoclinic	monoclinic
space group	$P\bar{1}$ (No.2)	$P\bar{1}$ (No.2)	$P2_1/c$ (No.14)	$P2_1/c$ (No.14)
a, Å	13.265(3)	6.244(1)	10.012(1)	15.204(4)
b, Å	15.438(3)	13.109(1)	12.676(1)	15.008(1)
c, Å	17.626(4)	13.605(1)	13.919(1)	10.463(2)
α, deg	88.91(1)	101.46(1)		
β, deg	68.80(1)	93.77(1)	106.15(1)	101.05(2)
γ, deg	72.56(1)	91.35(1)		
V, Å^3	3195(1)	1088.3(1)	1696.8(2)	2343.2(8)
Z	4	2	4	4
ϱ calc, g cm^{-3}	1.44	1.32	1.33	1.41
μ, mm^{-1}	0.41	0.76	0.65	1.75
F(000)	1424	452	712	1032
diffractometer	Nicolet R3m	Enraf–Nonius CAD4	Enraf–Nonius CAD4	Enraf–Nonius CAD4
radiation	Mo Kα	Cu Kα	Cu Kα	Cu Kα
λ, Å	0.71073	1.54178	1.54178	1.54178
max 2Θ, deg	50	140	120	120
no. of unique data	11237	4130	2506	3466
full-matrix least-squares refinement on no. of variables/restraints	F^2 847/6	F 293/1	F^2 239/2	F^2 328/0
R [for $I > 2\sigma(I)$]	0.046	0.066[b]	0.040	0.052
$wR2$	0.122		0.120	0.158
g_1/g_2	0.0628/0		0.0598/0.3622	0.0901/0.0831

[a] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$ with $w = 1/[\sigma^2(F_o^2) + (g_1P)^2 + g_2P]$ and $P = (F_o^2 + 2F_c^2)/3$. [b] For 3284 reflections $F > 3\sigma(F)$, $R_w = 0.073$; $R_w = \Sigma(|F_o| - |F_c|)w^{1/2}/\Sigma|F_o|w^{1/2}$ and $w = 1/[\sigma^2(F_o) + 0.0005F_o^2]$.

the 1*H*,2*H*-pyrazolo[3′,4′:4,5]pyrimido[6,1-*a*]phthalazines and -phthalazinium Ions. A stirred suspension of the iminophosphorane **1** (500 mg, 1.3 mmol) and the hetarene in dry acetonitrile was treated with the isocyanate and refluxed for the period given below. The solvent was distilled off *in vacuo* and the deeply colored oily residue was treated with a small amount of hot ethanol to afford in some cases a crude solid. Molar ratios, further purification, and the reaction times (in parentheses) are described below.

5-(Phenylamino)-1,2-dihydro-3-ethylpyrazolo[3′,4′:4,5]-pyrimido[6,1-*a*]phthalazine (4a). Phenylisocyanate (360 mg, 3 mmol) and phthalazine (400 mg, 3 mmol) were added to the imino-phosphorane **1** and heated to reflux temperature (3h). On cooling to room temperature a light yellow solid (**4a**) was obtained. More of **4a** together with N,N′-diphenylurea precipitated from the concentrated ethanolic solution. Chromatography of the collected solids on silica eluting with petroleum ether/ethyl acetate 1:5 afforded light yellow platelets, yield 115 mg (11%); mp 192–195 °C; IR (KBr) 3340, 3025, 2975, 1595, 1575, 1550, 1520 cm^{-1}; ^{1}H NMR (250 MHz) ($CDCl_3$) δ 1.45 (t, 3), 4.2 (q, 2), 5.7 (s, 1), 7.2–7.6 (m, 9), 7.85 (s, 1), 8.35 (s, 1); ^{13}C NMR (60.25 MHz) (DMSO) δ 15.06, 41.91, 54.47, 95.77, 121.08, 123.53, 124.62, 127.64, 128.35, 128.68, 131.40, 132.21, 134.26, 137.35, 143.18, 146.32; EIMS (70 eV) *m/z* (rel inten) 342 (M^+, 52); HRMS calcd for $C_{20}H_{18}N_6$ *m/z* 342.1593, found 342.1584.

5-(Phenylamino)-3-ethylpyrazolo[3′,4′:4,5]pyrimido-[6,1-*a*]phthalazinium Ion (5a). The residue of the concentrated ethanolic solution obtained above was chromatographed on silica eluting with petroleum ether/ethyl acetate, 2:15, affording an intense yellow amorphous solid which remained on the adsorbent bed and could be isolated by Soxhlet extraction with ethanol: yield 209 mg (47%); mp 204–205 °C; IR (KBr) 3350, 3050, 2980, 2930 cm^{-1}; ^{1}H NMR (90 MHz) (DMSO) δ 1.4 (t, 3, J = 7.1 Hz), 4.35 (q, 2, J = 7.0 Hz), 7.6 (s, 1), 7.2–7.7 (m, 3), 7.9 (d, 2, J = 7.9 Hz), 8.4 (m, 2), 8.75 (d, 1, J = 7.5 Hz), 9.4 (d, 1, J = 8.1 Hz), 9.5 (s, 1), 9.9 (s, 1); ^{13}C NMR (50 MHz) (DMSO) δ 14.23, 45.15, 102.17, 123.6, 124.66, 124.79, 125.68, 128.81, 128.9, 129.98, 136.97, 136.97, 137.04, 137.39, 143.67, 148.18, 148.54, 149.18; EIMS (70 eV), *m/z* (rel inten) 340 (M^+, 94); HRMS calcd for $C_{20}H_{16}N_6$ *m/z* 340.1436, found 340.1440.

5-[(4-Chlorophenyl)amino]-1,2-dihydro-3-ethylpyrazolo-[3′,4′:4,5]pyrimido[6,1-*a*]phthalazine (4b). 4-Chlorophenyl isocyanate (460 mg, 3 mmol) and phthalazine (400 mg, 3 mmol) were used (3 h). On cooling to room temperature a light yellow solid (**4b**) precipitated which was filtered off. More of compound **4b** together with *N,N′*-bis(4-chlorophenyl)urea were obtained from the concentrated ethanolic solution. Column chromatography of the collected solids on silica eluting with petroleum ether/ethyl acetate, 1:5, afforded yellow platelets: yield 145 mg (13%); mp 187 °C dec; IR (KBr) 3360, 3020, 2970, 1590, 1570, 1545, 1520 cm^{-1}; UV-vis (CH_2Cl_2) λ (log ϵ) 287 (3.24) nm; ^{1}H NMR (250 MHz) (DMSO) δ 1.35 (t, 3, J = 7.26 Hz), 4.05 (q, 2, J = 7.25 Hz), 5.75 (s, 1), 7.35 (d, 2, J = 8.6 Hz), 7.45–7.65 (m, 4), 7.7 (s, 1), 7.85 (d, 2, J = 8.6 Hz), 8.2 (s, 1), 9.15 (s, 1); ^{13}C NMR (60.25 MHz) (DMSO) δ 15.08, 41.11, 54.05, 95.61, 122.41, 123.40, 124.35, 125.08, 126.14, 128.12, 128.46, 131.55, 132.19, 134.16, 138.13, 142.24, 143.69, 146.79; EIMS (70 eV) *m/z* (rel inten) 376 (M^+, 57); HRMS calcd for $C_{20}H_{17}ClN_6$ *m/z* 376.1203, found 376.1153. Anal. Calcd for $C_{20}H_{17}ClN_6$: C, 63.74; H, 4.55; N, 22.30. Found: C, 64.18; H, 4.60; N, 21.88.

5-[(4-Chlorophenyl)amino]-3-ethylpyrazolo[3′,4′:4,5]-pyrimido[6,1-*a*]phthalazinium Ion (5b). The residue of the concentrated ethanolic solution obtained above was chromatographed on silica eluting with petroleum ether/ethyl acetate, 2:15, to give a deep yellow solid which remained on the adsorbent bed and could be isolated by Soxhlet extraction with ethanol; yield 233 mg (48%); mp 213–214 °C; IR (KBr) 3320, 3050, 2970, 2930 cm^{-1}; UV-vis (CH_2Cl_2) λ (qualitative) 480, 310, 265 nm; ^{1}H NMR (90 MHz) (DMSO) δ 1.45 (t, 3, J = 7 Hz), 4.4 (q, 2, J = 7 Hz), 7.4 (s, 1), 7.55 (d, 2, J = 7.5 Hz), 7.9 (d, 2, J = 7.3 Hz), 8.4 (t, 1, J = 8.1 Hz), 8.45 (t, 1, J = 8.1 Hz), 8.6 (d, 1, J = 8.0 Hz), 9.35 (d, 1, J = 7.9 Hz), 9.5 (s, 1), 9.88 (s, 1); ^{13}C NMR (50 MHz) (DMSO) δ 14.11, 42.01, 102.19, 119.14, 124.36, 124.55, 128.53, 128.62, 129.57, 135.77, 136.17, 136.86, 137.26, 138.56, 143.18, 148.13, 149.25, 152.31; EIMS (70 eV) *m/z* (rel inten) 374 (M^+, 100); HRMS calcd for $C_{20}H_{15}ClN_6$ *m/z* 374.1046, found 374.1044.

5-[(4-Chlorophenyl)amino]-3-ethylpyrazolo[3′,4′:4,5]-pyrimido[6,1-*a*]phthalazinium Betaine (6b). A solution of 24 mg (0.15 mmol) $KMnO_4$ in 10 mL of H_2O was added dropwise to a solution of 60 mg (0.15 mmol) of **5b** in 10 mL of ethanol and stirred for 5 h at room temperature. The precipitate (MnO_2) was filtered off and extracted three times with CH_2Cl_2. The mother liquor was extracted twice with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and the solvent was distilled off *in vacuo*. Column chromatography on silica (petroleum ether/ethyl acetate, 2:15) afforded a deep red solid: yield 50 mg (89%); mp 205–206 °C; IR (KBr) 3040, 2975, 2945, 1630, 1565, 1540 cm^{-1}; UV-vis (1,4-

dioxane) λ (log ϵ) 502 (2.87), 362 (3.18), 304 (3.29) nm; ^{1}H NMR (250 MHz) (DMSO) δ 1.35 (t, 3, J = 7 Hz), 4.05 (q, 2, J = 7 Hz), 7.25 (d, 2, J = 8.3 Hz), 7.3 (d, 2, J = 8.3 Hz), 8.1–8.25 (m, 2), 8.3 (d, 1 J = 6.8 Hz), 8.75 (s, 1), 8.95 (d, 1, J = 7.28 Hz), 9.3 (s, 1); ^{13}C NMR (60.25 MHz) (DMSO) δ 14.03, 40.37, 98.12, 120.82, 123.89, 124.68, 125.06, 125.48, 127.88, 128.22, 134.49, 135.39, 135.69, 143.25, 146.77, 149.02, 149.09, 151.90; EIMS (70 eV), *m/z* (rel inten) 374 (M^+, 100); HRMS calcd for $C_{20}H_{15}ClN_6$ *m/z* 374.1046, found 374.1046.

5-(Phenylamino)-3-ethylpyrazolo[3′,4′:4,5]pyrimido-[6,1-*a*]isoquinolinium Betaine (11a). Phenyl isocyanate (360 mg, 3 mmol) and isoquinoline (400 mg, 3 mmol) were added to the iminophosphorane **1** and heated to reflux temperature (3 h). The crude product was purified twice chromatographically on silica ((i) petroleum ether/ethyl acetate, 2:1, (ii) petroleum ether/ethyl acetate, 2:15) and then recrystallized from acetonitrile to give dark red-violet needles: yield 178 mg (41%); mp 207–208 °C; IR (KBr) 3040, 2980, 2940, 1630, 1570, 1540 cm^{-1}; UV-vis (1,4-dioxane) λ (log ϵ) 507 (2.94), 364 (3.39), 307 (3.64), 281 (3.70); ^{1}H NMR (90 MHz) (DMSO) δ 1.38 (t, 3, J = 7 Hz), 4.15 (q, 2, J = 7 Hz), 6.9 (m, 1), 7.25 (t, 2, J = 7.5 Hz), 7.45 (d, 2, J = 7.5 Hz), 7.78 (d, 1, J = 7.75 Hz), 7.9 (t, 1, J = 6.89 Hz), 8.06 (m, 2), 8.75 (s, 1), 9.05 (d, 1, J = 8.3 Hz), 9.7 (d, 1, J = 7.76 Hz); ^{13}C NMR (60.25 MHz) (DMSO) δ 14.09, 42.28, 99.34, 118.17, 121.78, 123.52, 124.20, 127.02, 127.54, 128.12, 128.32, 128.77, 134.27, 134.53, 135.60, 143.73, 146.03, 146.79, 152.56; EIMS (70 eV), *m/z* (rel inten) 339 (M^+, 93); HRMS calcd for $C_{21}H_{17}N_5$ *m/z* 339.1484, found 339.1493. Anal. Calcd for $C_{21}H_{17}N_5$: C, 74.32; H, 5.05; N, 20.63. Found: C, 74.08; H, 5.02; N, 20.79. The short distance between 1-H and 12-H has been demonstrated on the basis of a (qualitative) NOE experiment: Irradiation on 1-H caused on NOE amplification of the 12-H signal of about 23%.

5-[(4-Nitrophenyl)amino]-3-ethylpyrazolo[3′,4′:4,5]pyrimido[6,1-*a*]isoquinolinium Betaine (11b). 4-Nitrophenyl isocyanate (500 mg, 3 mmol) and isoquinoline (400 mg, 3 mmol) were heated together with **1** (3 h). The product was purified on a short silica column eluting with petroleum ether/ethyl acetate, 2:15. Due to its insolubility, the betaine remained on the adsorbent bed and could be isolated by Soxhlet extraction with acetone to give brilliant red crystals: yield 135 mg (27%); mp 293–294 °C; IR (KBr); UV-vis (1,4-dioxane) λ (qualitative) 557, 418, 366, 257 nm; ^{1}H NMR (250 MHz) (DMSO) δ 1.45 (t, 3, J = 7.2 Hz), 4.25 (q, 2, J = 7.2 Hz), 7.6 (d, 2, J = 6.9 Hz), 7.8 (m, 1), 7.9 (m, 1), 8.15 (m, 4) 8.9 (d, 1, J = 8.2 Hz), 9.1 (d, 1, J = 8.3 Hz), 9.75 (d, 1, J = 8.3 Hz); no ^{13}C NMR spectrum available because of insufficient solubility; EIMS (70 eV), *m/z* (rel inten) 384 (M^+, 51); HRMS calcd for $C_{21}H_{16}N_6O_2$ *m/z* 384.1335, found 384.1337. Anal. Calcd for $C_{21}H_{16}N_6O_2$: C, 65.62; H, 4.20; N, 21.86. Found: C, 65.66; H, 4.16; N, 21.08.

General Procedure for the Preparation of the Betaines 15 and 16. The isocyanate component was added to a stirred solution of the iminophosphorane **13** (500 mg, 1.1 mmol) in 5 mL of the dry hetarene as solvent and heated (max temp 130 °C) over the period given below. The excess hetarene was distilled off *in vacuo*. Unless otherwise noted, the colored residue was then treated with 20 mL of boiling ethanol to dissolve the triphenylphosphineoxide. Ethanol-soluble products crystallized on cooling. Molar ratios, purification, and reaction times (in parentheses) are described below.

5-[(4-Chlorophenyl)amino]-1,2-dihydro-3-methyl-1-oxo-2-phenylpyrazolo[3′,4′:4,5]pyrido[6,1-*a*]pyrimidinium Betaine (15a). 4-Chlorophenyl isocyanate (460 mg, 3 mmol) was heated together with **13** in dry pyridine (5 h). The crude solid was recrystallized from ethanol: yield 185 mg (42%); mp 236–238 °C; IR (KBr) 3060, 2975, 1670, 1615, 1595, 1565 cm^{-1}; UV-vis (1,4-dioxane) λ (log e) 428 (2.76), 341 (3.19), 288 (3.55) nm; ^{1}H NMR (250 MHz) (DMSO) δ 3.2 (s, 3), 7.3–7.6 (m, 10), 8.2–8.3 (m, 2), 9.7 (d, 1, J = 7 Hz); no ^{13}C NMR data available because of insufficient solubility; EIMS (70 eV) *m/z* (rel inten) 401 (M^+, 100); HRMS calcd for $C_{22}H_{16}ClN_5$ *m/z* 401.1044, found 401.1050. Anal. Calcd for $C_{22}H_{16}ClN_5$: C, 65.76; H, 4.01; N, 17.43. Found: C, 65.34; H, 4.17; N, 17.11.

5-[(4-Chloro-3-ethoxyphenyl)amino]-1,2-dihydro-3,9-dimethyl-1-oxo-2-phenylpyrazolo[3′,4′:4,5]pyrido[6,1-*a*]-pyrimidinium Betaine (15b). The treatment of **13** with 4-chloro-3-ethoxyphenyl isocyanate (650 mg, 3 mmol) in γ-picoline afforded a deep orange solid after recrystallization from ethanol: yield 223 mg (44%); mp 206 °C; IR (KBr) 3055, 2970, 1670, 1600, 1585 cm^{-1}; UV-vis (1,4-dioxane) λ (qualitative) 418, 346, 289 nm; ^{1}H NMR (250 MHz) (DMSO) δ 1.35 (t, 3, J = 6.5 Hz), 2.4 (s, 3), 3.1 (s, 3), 4.05 (q, 2, J = 6.5 Hz), 7.0 (d, 1, J = 7.4 Hz), 7.2–7.5 (m, 8), 7.9 (s, 1), 9.5 (d, 1, J = 7 Hz); ^{13}C NMR (60.25 MHz) (DMSO) δ 14.25, 15.08, 59.71, 83.18, 109.10, 109.66, 114.28, 119.85, 120.39, 122.72, 123.34, 126.16, 126.91, 128.62, 129.28, 135.95, 145.17, 146.00, 147.67, 153.38, 154.36, 160.57, 160.96; EIMS (70 eV) *m/z* (rel inten) 459 (M^+, 100); HRMS calcd for $C_{25}H_{22}ClN_5O_2$ *m/z* 459.1462, found 459.1456. Anal. Calcd for $C_{25}H_{22}ClN_5O_2$: C, 65.29; H, 4.82; N, 15.23. Found: C, 65.20; H, 4.73; N, 15.18.

5-[(4-Chlorophenyl)amino]-1,2-dihydro-3-methyl-1-oxo-2-phenylpyrazolo[3′,4′:4,5]pyrimido[6,1-*a*]isoquinolinium Betaine (16a). 4-Chlorophenyl isocyanate (460 mg, 3 mmol) was added to a suspension of **13** in isoquinoline (5 h). The oily residue was subsequently chromatographed on silica eluting with petroleum ether/ethyl acetate, 1:5, affording an orange-colored amorphous solid: yield 235 mg (47%); mp 227–228 °C; IR (KBr) 3065, 2970, 1690, 1645, 1600, 1570 cm^{-1}; UV-vis (1,4-dioxane) λ (qualitative) 428, 344, 272 nm; ^{1}H NMR (250 MHz) (DMSO) δ 3.2 (s, 3), 7.3–7.55 (m, 9); 7.7 (d, 1, J = 7.68 Hz), 7.8 (dd, 1, J = 7.87, 4.12 Hz), 8.0 (d, 2, J = 4.0 Hz), 9.5 (d, 1, J = 7.7 Hz), 10.6 (d, 1, J = 8.53 Hz); ^{13}C NMR (60.25 MHz) (DMF) δ 34.88, 89.23, 117.26, 125.13, 125.34, 126.19, 126.72, 127.28, 127.31, 127.35, 128.57, 128.75, 129.63, 132.91, 135.42, 135.93, 137.11, 148.21, 148.31, 151.07, 161.96, 162.09; EIMS (70 eV) *m/z* (rel inten) 451 (M^+, 100); HRMS calcd for $C_{26}H_{18}ClN_5O$ *m/z* 451.1200, found 451.1200. Anal. Calcd for $C_{26}H_{18}ClN_5O$: C, 69.10; H, 4.01; N, 15.50. Found: C, 68.87; H, 4.04; N, 15.60.

5-[(4-Chloro-3-ethoxyphenyl)amino]-1,2-dihydro-3-methyl-1-oxo-2-phenylpyrazolo[3′,4′:4,5]pyrimido[6,1-*a*]-isoquinolinium Betaine (16b). 4-Chloro-3-ethoxyphenyl isocyanate (600 mg, 3 mmol) was used. The oily residue was chromatographed on silica eluting with petroleum ether/ethyl acetate 1:5 to obtain deep orange crystals after recrystallization from ethanol: yield 285 mg (52%); mp 216–218 °C; IR (KBr) 3060, 2975, 1670, 1615, 1590 cm^{-1}; UV-vis (1,4-dioxane) λ (log ϵ) 430 (2.92), 340 (3.40), 273 (3.65) nm; ^{1}H NMR (250 MHz) (DMSO) δ 1.35 (t, 3, J = 6.9 Hz), 3.2 (s, 3), 4.1 (q, 2, J = 6.9 Hz), 7.0 (dd, 1, J = 8.51, 2 Hz), 7.2–7.6 (m, 9), 7.7 (d, 1, J = 7.87 Hz), 7.75 (dd, 1, J = 7.8, 4.23 Hz), 8.0 (d, 2, J = 3.92 Hz), 9.5 (d, 1, J = 7.6 Hz, 10.6 (d, 1, J = 8.6 Hz); no ^{13}C NMR data available because of insufficient solubility; EIMS (70 eV) *m/z* (rel inten) 495 (M^+, 73); HRMS calcd for $C_{28}H_{22}ClN_5O_2$ *m/z* 495.1462, found 495.1455. Anal. Calcd for $C_{28}H_{22}ClN_5O_2$: C, 67.81; H, 4.47; N, 14.12. Found: C, 67.74; H, 4.51; N, 13.63.

Preparation of the 8-(4-Ethoxyphenyl)-3-ethyl-5-(phenylamino)-3*H*,7*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[1,2-*a*][1,2,4]-triazine-7,9(8*H*)-dione (9a). To a stirred solution of the pyrazoleiminophosphorane **1** (500 mg, 1.3 mmol) and phenyl isocyanate (360 mg, 3 mmol) in 10 mL of dry CH_2Cl_2 under an argon atmosphere was added dropwise a solution of 4-(4-ethoxyphenyl)-TAD (650 mg, 3 mmol) in 10 mL of the solvent at a temperature of −15 °C until the color persisted. The solvent was distilled off *in vacuo* and the brown oily residue was treated with hot ethyl acetate to give the crude product which was purified by silica chromatography eluting with petroleum ether/ethyl acetate 2:15 to give colorless needles after recrystallization from ethyl acetate: yield 60 mg (11%); mg (11%); mp 184 °C; IR (KBr) 3250, 3100, 2980, 2930, 1760, 1690 cm^{-1}; UV-vis (1,4-dioxane) λ (log ϵ) 255 (3.49); ^{1}H NMR (250 MHz) ($CDCl_3$) δ 1.45 (t, 3, J = 7.2 Hz), 1.5 (t, 3, J = 7.3 Hz), 4.05 (q, 2, J = 7.15 Hz), 4.15 (q, 2, J = 7.3 Hz), 7.0 (d, 2, J = 6.9 Hz), 7.15 (t, 1, J = 7.3 Hz), 7.4 (m, 4), 7.55 (s, 1), 7.6 (d, 2, J = 7.7 Hz), 9.75 (s, 1); ^{13}C NMR (60.25 MHz) ($CDCl_3$) δ 15.41, 15.68, 43.61, 64.54, 104.88, 115.97, 121.38, 122.62, 124.50, 125.38, 128.01, 129.84, 137.38, 140.93, 143.46, 147.09, 160.11; EIMS (70 eV), *m/z* (rel inten) 431 (M^+, 100); HRMS calcd for $C_{22}H_{21}N_7O_3$ *m/z* 431.1706, found 431.1711. Anal.

Calcd for $C_{22}H_{21}N_7O_3$: C, 61.24; H, 4.91; N, 22.72. Found: C, 60.93; H, 4.42; N, 22.33.

8-(4-Chlorophenyl)-3-ethyl-5-(phenylamino)-3*H*,7*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[1,2-*a*][1,2,4]triazine-7,9-(8*H*)dione (9b). As described above for compound **9a**, 4-chlorophenyl-TAD (500 mg, 3 mmol) and phenyl isocyanate (360 mg, 3 mmol) were added to the iminophosphorane **2** (500 mg, 1.3 mmol). The crude residue was recrystallized from a small amount of warm ethyl acetate to give colorless needles: yield 65 mg (12%), mp 229–230 °C; IR (KBr) 3225, 3080, 2980, 2925, 1765, 1690 cm^{-1}; UV-vis (1,4-dioxane) λ (log ϵ) 339 (2.86), 247 (3.47) nm; ^1H NMR (250 MHz) (DMSO) δ 1.35 (t, 3, J = 7.25 Hz), 4.05 (q, 2, J = 7.21 Hz), 7.4–7.6 (m, 8), 7.7 (d, 2, J = 7 Hz) 9.8 (s, 1); ^{13}C NMR (60.25 MHz) (DMSO) δ 14.80, 42.11, 104.46, 122.21, 122.86, 126.70, 127.93, 128.825, 128.96, 129.13, 130.30, 134.04, 135.80, 140.71, 143.14, 146.67; EIMS (70 eV) *m/z* (rel inten) 421 (M^+, 100); HRMS calcd for $C_{20}H_{16}ClN_7O_2$ *m/z* 421.1054, found 421.1053. Anal. Calcd for $C_{20}H_{16}ClN_7O_2$: C, 56.95; H, 3.82; N, 23.24. Found: C, 56.77; H, 3.92; N, 22.86.

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