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Comparative Studies on the Behavior of 3-Amino-2-phenyl-4(3*H*)-quinazolinone Towards Some Organophosphorus Reagents

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Summary. The reaction of 3-amino-2-phenyl-4(3*H*)-quinazolinone with oxovinylidenetriphenylphosphorane afforded 5-phenylpyrazolo[1,5-*c*] quinazoline-2(3*H*)-one and triphenylphosphine oxide. On the other hand, when quinazolinone reacts with phosphorus ylides, the corresponding phosphorane adducts were obtained. Moreover, quinazolinone reacts with trisdialkylaminophosphines to give the new (dialkylamino)oxophosphonium dipolar products. Possible reaction mechanisms are considered and the structural assignments are based on analytical and spectroscopic results.

Keywords. Oxovinylidenetriphenylphosphorane; Ylides; Tris(dialkylamino)phosphines; 4(3*H*)-Quinazolinone.

Introduction

In recent years there has been an increasing interest in the chemistry of 4(3*H*)-quinazolinones because of their biological significance. Many of them show antifungal, antibacterial, anticancer, antiinflammatory, anticonvulsant, immunotropic, hypolipidemic, antitumor, antiulcer analgesic, and antiproliferative activities [1–9]. This together with our interest in organophosphorus chemistry [10–14] enhanced the synthesis of new phosphorus compounds incorporating such important nuclei that may possibly lead to further biological activity. The present study deals with the reaction of an active phosphacumulene ylide, namely 2-oxovinylidenetriphenylphosphorane (**2**) with 3-amino-2-phenyl-3*H*-quinazoline-4-one (**1**) and a comparison of the reactivity of the active phosphacumulene **2** with the reactivity of stabilized phosphonium ylides **3a–3d** and tris(dialkylamino)-phosphines **4a** and **4b** towards the above mentioned quinazolinone **1** (Scheme 1).

Results and Discussion

We found that 3-amino-2-phenyl-4(3*H*)-quinazolinone (**1**) reacts with one mol equivalent of 2-oxovinylidenetriphenylphosphorane (**2**) in dry tetrahydrofuran at room temperature for 10 h to give a colorless crystalline product assigned structure **5**. Triphenylphosphine oxide was also isolated from the reaction mixture. Structural support for 5-phenylpyrazolo [1,5-*c*]quinazoline-2(3*H*)-one was based upon correct elemental analysis, IR, ^{1}H, ^{13}C NMR, and mass spectral data (*cf.* Experimental and Scheme 2).

A possible explanation for the course of the reaction of 2-oxovinylidenetriphenylphosphorane (**2**) with **1** is shown in Scheme 2. Formation of adduct **5** can be explained in terms of addition of the ylide **2** to the acidic *Y*–H bond followed by cyclization with expulsion of triphenylphosphine oxide [15]. In addition, we studied the behavior of the 4(3*H*)-quinazolinone **1** towards the resonance stabilized ylidenetriphenylphosphoranes **3a–3d**. The reaction of **1** with ethoxycarbonylmethylenetriphenylphosphorane (**3a**) proceeded in boiling dry toluene with the formation of the new phosphorane product **6** as the sole reaction product. Triphenylphosphine and/or triphenylphosphine oxide could be neither isolated nor

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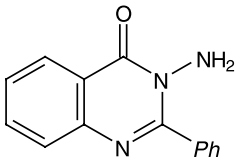
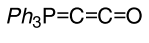


1



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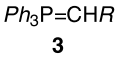


3

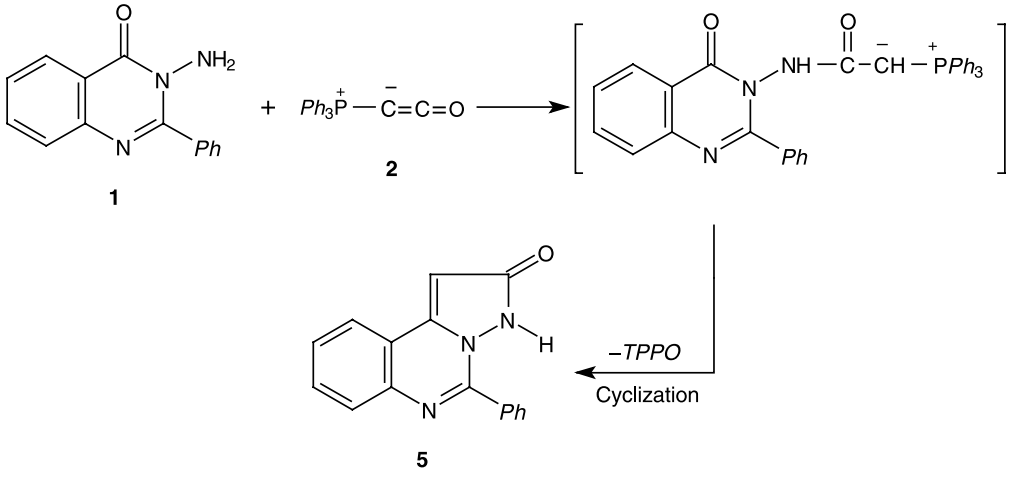
a, *R* = COO*Et*
b, *R* = COO*Me*
c, *R* = CHO
d, *R* = CN

4

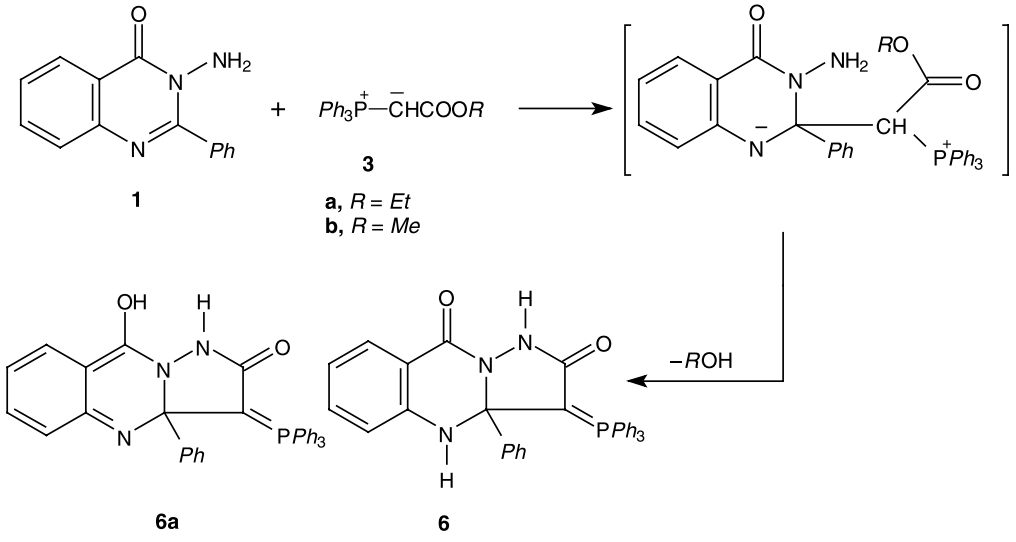
a, *R* = *Me*; **b,** *R* = *Et*

Scheme 1

detected in the reaction medium (Scheme 3). Similarly, compound **1** reacts with methoxycarbonylmethylenetriphenylphosphorane (**3b**) in a 1:1 molar ratio to give the same product **6** in 80% yield (*cf.* Experimental). The structure of 3a-phenyl-3-(triphenylphosphoranylidene)-3a,4-dihydropyrazolo[5,1-*b*] quinazolin-2,9(1*H*,3*H*)-dione (**6**) is deduced from its spectroscopic data. Mass spectrum and elemental analysis of compound **6** indicated that the reaction results in a 1:1 condensative cyclization accompanied by extrusion of the appropriate alcohol molecule (Scheme 3). Structure **6** ($\delta_P = +26.21$ ppm) was established on the basis of IR, ^{1}H, and ^{13}C NMR spectra (*cf.* Experimental). The presence of a doublet



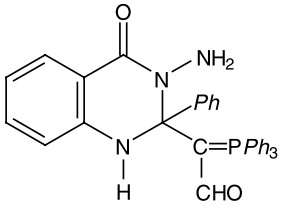
Scheme 2



Scheme 3

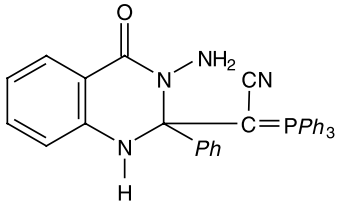
centered at 168.59 (d, *CO*–C=P*Ph*$_3$) with $^2J_{CP}$ = 33.7 Hz and a singlet at 164.96 (Ar–*CO*–N) for the two carbonyl groups in the ^{13}C NMR spectrum of compound **6** confirmed structure **6** and excludes an alternative structure **6a**.

Next, the reaction of **1** with (triphenylphosphoranylidene)acetaldehyde (**3c**) was investigated. We found that the reaction of **3c** with **1**, in dry toluene, proceeds at reflux temperature to give chromatographically pure 1:1 adduct formulated as (3-amino-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinazolin-2-yl)-(triphenylphosphoranylidene)acetaldehyde (**7**).



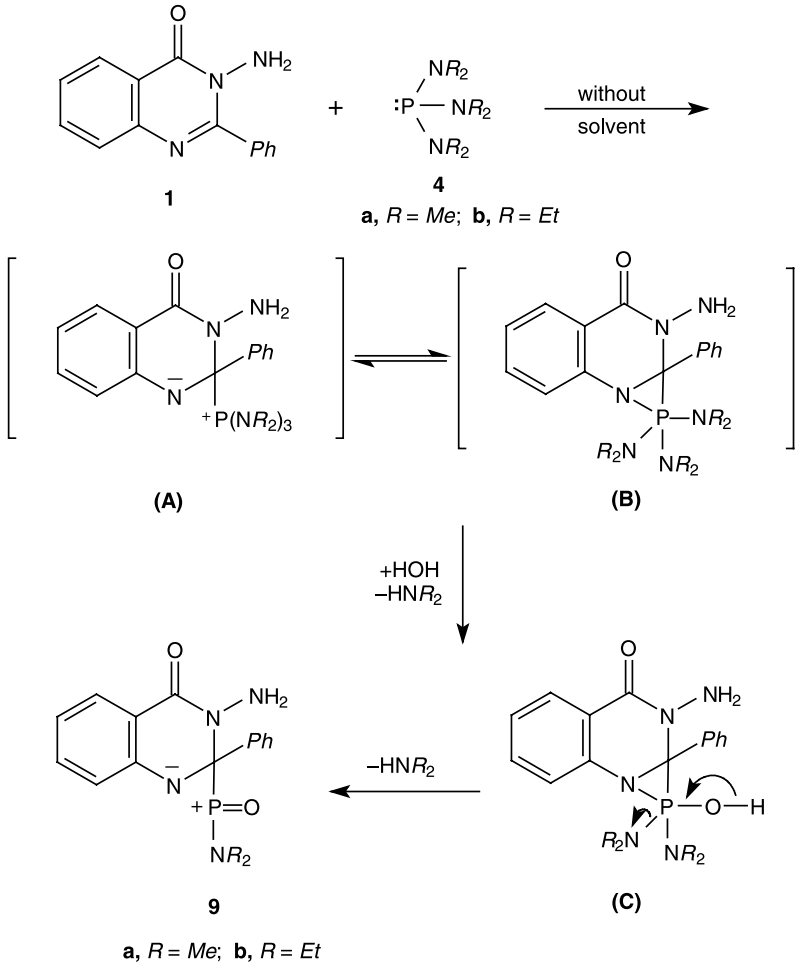
7

The structure of compound **7** is deduced from its elemental analysis, IR, ^{1}H NMR, and mass spectral data (*cf.* Experimental). Similarly, (3-amino-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinazolin-2-yl)(triphenylphosphoranylidene)acetonitrile (**8**) was obtained from the reaction of **1** with cyanomethylenetriphenylphosphorane (**3d**). The structure of compound **8** was deduced from correct microanalysis, IR, ^{1}H NMR, and mass spectral data (*cf.* Experimental).



8

Furthermore, this study was extended to include the behavior of **1** towards trisdialkylaminophosphines **4a** and **4b** to determine the preferential site of attack.



1 + **4** (**a**, *R* = *Me*; **b**, *R* = *Et*) → **(A)** ⇌ **(B)** → **(C)** → **9** (**a**, *R* = *Me*; **b**, *R* = *Et*)

Scheme 4

We found that tris(dialkylamino)phosphines **4a** and **4b** reacted with 3-amino-2-phenyl-4(3*H*)-quinazolinone (**1**) only at 110°C (without solvent) to give pure adducts formulated as **9a** and **9b** (Scheme 4).

Supplementary evidence for the assigned structure **9a** was gained from elemental analysis, IR, ^{1}H, ^{31}P, ^{13}C NMR, and mass spectral data. The IR spectrum of **9a**, in KBr, revealed the presence of an intense band at 1240 cm^{-1} (P=O) absorption [16], two bands at 1320 and 860 cm^{-1} due to the absorption of P–$N(CH_3)_2$ [17], at 1656 cm^{-1} (C=O), and at 3230 cm^{-1} (NH_2). Moreover, the IR spectrum of **9a** showed the absence of the absorption band at 1580 cm^{-1} (C=N). The ^{1}H NMR spectrum of **9a** gave a doublet centered at $\delta = 2.43$ ppm ($J_{HP} =$ 10 Hz) due to the 6H of the dimethyl amino group, two singlets at 8.65 and 8.68 ppm (NH_2), and a multiplet at 7.05–7.62 ppm (Ar, 9H). The ^{31}P NMR shift recorded for adduct **9a** was +50.76 ppm. This value favours the open dipolar ion structure (**9a**) [18, 19] (*cf.* Scheme 4). The ^{13}C NMR spectrum of **9a** adds good support for the proposed structure which reveals the carbonyl carbon as singlet at 165.64 ppm, the quaternary carbon attached to the phosphorus at 67.36 ppm, 25.72, 25.72 ppm due to the dimethylamino group (cf. Experimental). Moreover, elemental analyses and molecular weight determination (MS) of **9a** support the molecular formula.

Similarly, compound **1** reacts with tris(diethylamino)phosphine (**4b**) to give a colorless crystalline compound formulated as **9b** (Scheme 4). A possible explanation for the reaction of **1** with tris(dialkylamino)phosphines **4a** and **4b** is shown in Scheme 4. Thus, initial attack of aminophosphines **4** on the most reactive center of **1** leads to the formation of the dipolar adduct **A** that undergoes ring closure giving compound **B**. The latter could collapse [20a, b] to the most stable form **9** through the rapid hydrolysis of **B** (by the presence of unavoidable moisture) to give the intermediate **C**, which undergoes further decomposition [20a, b], yielding the open dipolar structures **9a** and **9b** (through expulsion of two moles of dimethylamine; Scheme 4).

Conclusion

From the results of the present investigation, it could be concluded that the reaction course of 3-amino-2-phenyl-4(3*H*)-quinazolinone (**1**) with active phosphacumulene **2** differs markedly from that of the respective stabilized phosphonium ylides **3a**–**3d**. In the case of the reaction of quinazolinone (**1**) with phosphacumulene **2**, 5-phenylpyrazolo[1,5-*c*]-quinazoline-2(3*H*)-one (**5**) was produced.

Moreover, the reaction of **1** with stabilized phosphonium ylides leads to different products depending on the reaction conditions as well as the stability of the addition products. Also, the behavior of **1** towards tris(dialkylamino)phosphines **4a** and **4b** resulting in the formation of the open dipolar structure **9**, which greatly predominated over the cyclic structure. The significance of these results represents a new finding supplementing the promising aspects of utilizing certain phosphorus reagents in syntheses.

Experimental

Melting points were measured by means of an electrothermal apparatus. Phosphoranes **3a**–**3d** and 3-amino-2-phenyl-3*H*-quinazoline-4-one (**1**) were prepared according to Refs. [21, 22]. The IR spectra were measured in KBr pellets with a Perkin-Elmer Infrared Spectrophotometer Model 157. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, with a Varian Spectrometer at 270 and 67.5 MHz using *TMS* as internal reference. The ^{31}P NMR spectra were taken with a Varian CFT-20 (*vs.* external 85% H_3PO_4 standard). The mass spectra were recorded at 70 eV with a Kratos MS equipment or Varian MAT 311 A Spectrometer. Elemental analyses were performed using the Elmentar Varu EL Germany Instrument. Their values agreed favourably with the calculated ones.

*Reaction of Phosphacumulene Ylide **2** with 3-Amino-2-phenyl-3H-quinazoline-4-one* (**1**)

A mixture of 0.30 g **2** (1 mmol) and 0.23 g **1** [21, 22] (1 mmol) in 30 cm^3 *THF* was stirred at room temperature for 10 h. The volatile materials were evaporated under reduced pressure. The residue was subjected to silica gel column chromatography to give **5**.

5-Phenylpyrazolo[1,5-c]quinazoline-2(3H)-one (**5**, $C_{16}H_{11}N_3O$)

Eluent: petroleum ether/ethyl acetate (25/75, *v*/*v*). Product **5** was separated as colorless crystals, yield 85%; mp 234°C; IR (KBr): $\bar{\nu} = 1664$ (CONH), 1630 (C=N), 3256 (NH) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 6.70$ (s, 1H, C=C*H*–CO), 7.20–7.62 (m, 9H, Ar), 8.70 (s, NH) ppm; ^{13}C NMR (270 MHz, $CDCl_3$): $\delta = 165.55$ (C=O), 96.49 (C=*CH*–C=O), 160.30 (*C*=CH–CO), 163.40 (*C*=N), 128.40, 150.97 (C=C, Ar), 126.82, 127.35, 128.72, 121.61 (4CH–CH, Ar), 128.30 (*C*–CH, Ar), 126.20 (C–*CH*, Ar) ppm; MS (EI): m/z (%) = 261 (M^+, 95).

Triphenylphosphine oxide was also separated (mix mp, MS).

Reaction of Compound **1** *with Ethoxycarbonylmethylene triphenylphosphorane* (**3a**)

A mixture of 1 mmol **1** and 1 mmol phosphonium ylide **3a** in 30 cm^3 dry toluene was refluxed for 6 h. The volatile materials were evaporated under reduced pressure. The residue was subjected to silica gel column chromatography to give **6**.

3a-Phenyl-3-(triphenylphosphoranylidene)-3a,4-dihydropyrazolo[5,1-b]-quinazolin-2,9(1H,3H)-dione (**6**, $C_{34}H_{26}N_3O_2P$)

Eluent: petroleum ether/acetone (70/30, *v*/*v*). Product **6** was separated as white crystals, yield 80%; mp 221°C; IR (KBr): $\bar{\nu} = 1666$ (*CO*–NH), 3254 (b, 2NH), 1680, 1510 (C=P) and at 1430, 990 (P–C, phenyl) [23] cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 6.61$–7.30 (m, 24H, Ar), 8.55, 8.64 (d, 2H, NH, $J_{HP} = 8$ Hz) ppm; ^{13}C NMR (270 MHz, $CDCl_3$): $\delta = 122.29$ (d, $^1J_{CP} = 124.45$ Hz, *C*=P), 168.59 (d, $^2J_{CP} = 33.7$ Hz, *C*=O), 164.96 (s, *C*=O), 128.22, 116.70, 132.25, 113.53 (4CH, Ar), 115.13, 147.25 (C=C, Ar), 144.52, 127.10, 128.32, 126.25 (4CH, *Ph*), 128.74, 131.30, 128.52, 129.03 (P*Ph*$_3$) ppm; ^{31}P NMR (270 MHz, $CDCl_3$): $\delta = +26.21$ ppm; MS (EI): m/z (%) = 539 (M^+, 90).

Similarly, product **6** was obtained by the reaction of methoxycarbonylmethylenetriphenylphosphorane (**3b**) with **1**.

General Procedure for the Reaction of Phosphonium Ylides ***3c***, ***3d*** *with Quinazolinone* ***1***

A mixture of 1 mmol **3c** and **3d** and 1 mmol quinazolinone **1** in 30 cm^3 dry toluene was refluxed for 8 h. The volatile materials were evaporated under reduced pressure. The residue was subjected to silica gel column chromatography to give products **7** and **8**.

(3-Amino-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinazolin-2-yl)-(triphenylphosphoranylidene)acetaldehyde (**7**, $C_{34}H_{28}N_3O_2P$)

Eluent: petroleum ether/acetone (85/15, *v*/*v*). Product **7** was separated as colorless crystals, yield 75%; mp 237°C; IR (KBr): $\bar{\nu} = 1718$ (C=O, aldehyde), 1656 (C=O, O=C–N–NH_2) 1674, 1530 (C=P), 1448, 928 (P–C, phenyl), 3230 (NH_2), 3254 (NH) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 9.95$ (d, 1H, O=*CH*–C=P, $^2J_{HP} = 30$ Hz), 8.30 (d, 1H, NH, $^4J_{HP} = 10$ Hz), 8.65, 8.70 (2s, NH_2), 6.90–7.90 (m, 24H, Ar) ppm; ^{13}C NMR (270 MHz, $CDCl_3$): $\delta =$ 193.05 (d, $^2J_{CP} = 27.0$ Hz, *C*HO), 115.30 (d, $^1J_{CP} = 120$ Hz, *C*=PPh_3), 54.73 (d, $^2J_{CP} = 25.0$ Hz, *C*–C=P), 164.52 (N*C*=O), 113.37, 113.23, 117.45, 128.50 (4CH, Ar), 115.35, 147.43 (C=C, Ar), 144.32, 127.23, 128.42, 126.50 (*Ph*), 128.37, 132.05, 129.13, 127.05 (P*Ph*$_3$) ppm; ^{31}P NMR (270 MHz, $CDCl_3$): $\delta = +22.7$ ppm; MS (EI): m/z (%) = 541 (M^+, 90).

(3-Amino-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinazolin-2-yl)(triphenylphosphoranylidene)acetonitrile (**8**, $C_{34}H_{27}N_4OP$)

Eluent: petroleum ether/ethyl acetate (50/50, *v*/*v*). Product **8** was separated as colorless crystals, yield 80%; mp 243°C; IR (KBr): $\bar{\nu} = 1660$ (C=O, O=C–N–NH_2) 2200 (CN), 3250 (NH), 1686, 1515 (C=P), 1432, 985 (P–C, phenyl) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 8.72$, 8.75 (2s, NH_2), 8.43 (d, NH, $^4J_{HP} = 10$ Hz), 6.72–7.35 (m, Ar) ppm; ^{13}C NMR (270 MHz, $CDCl_3$): $\delta = 118.2$ (*C* = N, $^2J_{CP} = 26.1$ Hz), 105.83 (*C* = P, $^1J_{CP} = 115$ Hz), 69.55 (N–*C*–N, $^2J_{CP} =$ 22.0 Hz), 165.22 (N*C*=O), 128.12, 117.15, 132.62, 112.65 (4CH, Ar), 117.31, 142.32 (C=C, Ar), 142.45, 127.12, 128.34, 126.52 (*Ph*), 128.37, 131.26, 129.05, 126.24 (PPh_3) ppm; ^{31}P NMR (270 MHz, $CDCl_3$): $\delta = +21.75$ ppm; MS (EI): m/z (%) = 538 (M^+, 100).

Reaction of Tris(dialkylamino)phosphines ***4a*** *and* ***4b*** *with 3-Amino-2-phenyl-4(3H)-quinazolinone* (**1**)

A suspension of 0.23 g **1** (1 mmol), 1 cm^3 tris(dialkylaminophosphines **4a** or **4b** was heated in an oil bath at 110°C for 8 h. The reaction mixture was evaporated under reduced pressure. The residue was subjected to silica gel column chromatography to give products **9a** and **9b**.

3-Amino-4-hydroxy-2-phenyl-3,4-dihydro-quinazolin-4-yl)-(dimethylamino)oxophosphonium (**9a**, $C_{16}H_{17}N_4O_2P$)

Eluent: petroleum ether/acetone (50/50, *v*/*v*). Product **9a** was separated as colorless crystals, yield 75%; mp 215°C; IR (KBr): $\bar{\nu} = 1580$ (C=N), 1240 (P=O), 1320, 860 [P–N$(CH_3)_2$] 3230 (NH_2) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 2.43$ [d, $J_{HP} = 10$ Hz, PN$(CH_3)_2$], 7.05–7.62 (m, 9H, Ar), 8.65, 8.68 (2s, NH_2) ppm; ^{13}C NMR (270 MHz, $CDCl_3$): $\delta = 165.64$ (*C*=O), 119.73 (=*C*–CO), 139.50 (=*C*–N), 76.46 (N–*C*–P), 25.72, 25.72 [P–$(NCH_3)_2$], 139.60, 128,63, 127,08, 127.43 (C_6H_5), 127.45, 119.50, 137.65, 115.34 (4CH, Ar) ppm; ^{31}P NMR (270 MHz, $CDCl_3$): $\delta = +50$ ppm; MS (EI): m/z (%) = 328 (M^+, 100).

3-Amino-4-hydroxy-2-phenyl-3,4-dihydro-quinazolin-4-yl)-(diethylamino)oxophosphonium (**9b**, $C_{18}H_{21}N_4O_2P$)

Eluent: petroleum ether/acetone (75/25, *v*/*v*). Product **9b** was separated as colorless crystals, yield 80%; mp 211°C; IR (KBr): $\bar{\nu} = 1585$, 1245 (P=O), 1315, 870 [P–N $(C_2H_5)_2$], 3240 (NH_2) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 1.94$ (t, 6H, P[N–CH_2CH_3)$_2$], 2.35 {q, 4H, P[N(CH_2CH_3)$_2$], $^3J_{HP} =$ 10 Hz}, 6.80–7.73 (m, 9H, Ar), 8.0, 8.15 (2s, NH_2) ppm; MS (EI): m/z (%) = 356 (M^+, 95).

References

[1] Bartroli J, Turmo E, Alguero M, Boncompte E, Vericat ML, Conte L, Ramis J, Merlos M, Garcia-Rafanell J, Forn (1998) J Med Chem **41**: 1869

[2] Shiba SA, El-Khamry AA, Shaban ME, Atia KS (1997) Pharmazie **52**: 189

[3] Abdel-Hamid SG (1997) J Ind Chem Soc **74**: 613

[4] Barker A (1995) J Eur Pat 635498; Chem Abstr **122**: 214099

[5] Bekhit AA, Khalil MA (1998) Pharmazie **53**: 539

[6] Gursoy A, Karali N (1995) Farmaco **50**: 857

[7] Nawrocka W, Zimecki M (1997) Arch Pharm **330**: 399

[8] Kurogi Y, Inoue Y, Tsutsumi K, Nakamura S, Nagao K, Yoshitsugu H, Tsuda Y (1996) J Med Chem **39**: 143
[9] Hamel E, Lin CM, Plowman J, Wang HK, Lee KH, Paull KD (1996) Bioorg Pharm **51**: 53
[10] Boulos LS, Abdel-Malek HA (2004) Phosph Sulf Silicon **179**: 97
[11] Boulos LS, Abdel-Malek HA (2005) Ind J Heterocycl Chem **14**: 245
[12] Boulos LS, Yakout El-Sayed MA, Arsanious MHN (2006) Phosph Sulf Silicon **181**: 1615
[13] Boulos LS, El-Din NK, Arsanious MHN (2006) Phosph Sulf Silicon **181**: 1467–1475
[14] Arsanious MHN, Boulos SL (2006) Monatsh Chem **137**: 1177
[15] Bestmann HJ, Schmid G, Sandmeier D (1976) Angew Chem **88**: 92; Angew Chem Int Ed Engl **5**: 115
[16] Bellamy LJ (1964) The Infrared Spectra of Complex Molecules. Wiley & Sons, New York, p 311
[17] Colthup NB, Daly LH, Wiberley SE (1964) Introduction to Infrared and Raman Spectroscopy. Academic press, New York, p 304
[18] Ramirez F, Patwardhan AV, Kugler HJ, Smith CP (1967) J Amer Chem Soc **89**: 6276
[19] Granoth I, Martin JC (1978) J Am Chem Soc **100**: 7434; (1979) **101**: 4618
[20] (a) El-Kateb AA, Boulos LS, Abd El-Malek HA (1993) Phosph Sulf Silicon **83**: 105; (b) Boulos LS, Arsanious HN (2001) Heteroatom Chem **12**: 511
[21] Bain DI, Smallay RK (1968) J Chem Soc (C): 1593
[22] Errede LA (1976) J Org Chem **41**: 1763
[23] Hesse M, Meier H, Zeeh B (1979) Spektroskopische Methoden in der Organischen Chemie. Thieme Verlag G Stuttgart