Synthesis of a 3,1-Benzoxazin-4-one, 2,4(1*H*,3*H*)-Quinolinediones, and 2,4(1*H*,3*H*)-Quinazolinediones from the Reaction of Phosphoryl-Stabilized Anions Containing no α-Hydrogen Atoms with Isatoic Anhydride

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Since isatoic anhydride **(1)** is a versatile reagent for the syntheses of heterocyclic compounds containing nitrogen atoms, its chemistry has been widely studied[1]. From this point of view, we have been interested in the reactivity of **1** toward phosphorus compounds. Although it is known that **1** reacts with a phosphonium ylid[2] and a phosphonate carbanion[3] to give a resonanced-stabilized ylid and a quinolylphosphonate derivative, no Wittig or Wittig-Horner reaction product is obtained. On the other hand, we previously reported that the reaction of **1** with an α-phosphono-γ-butyrolactone carbanion containing no hydrogen atoms on the α-carbon atom led to a benzoxazine derivative[4]. This result prompted us to investigate the reaction of **1** with phosphoryl-stabilized anions similarly bearing no α-hydrogen atoms.

The reaction of **1** with an ethyl 2-diethylphosphonopropanoate carbanion **(3a)** in refluxing benzene and benzene/dimethylformamide (4:1) for 5 h gave 2-(1-ethoxycarbonylethyl)-4*H*-3,1-benzoxazin-4-one **(4a)** and 3-ethoxycarbonyl-3-methyl-2,4(1*H*,3*H*)-quinolinedione **(5a)** in 64% and 4%, and 18% and 43% yields, respectively. In contrast, similar treatment of *N*-sodioisatoic anhydride **(2)**, prepared *in situ* from **1** and an equivalent amount of sodium hydride, with **3a** in the mixed solvent led exclusively to **5a** in 60% yield.

In comparison to **3a**, the reaction of **1** with ethyl 2-diethylphosphonobutanoate **(3b)** and ethyl 2-diethylphosphono-4-pentenoate carbanions **(3c)** in the mixed solvent gave no products corresponding to **4a** or **5a**, instead unreacted **1** was recovered. However, **2**, on similar treatment with **3b**, **3c**, or the ethyl 2-diethylphosphono-3-phenylpropanoate carbanion **(3d)**, afforded only the expected products, 3-ethyl- **(5b)**, 3-allyl- **(5c)**, and 3-benzyl-3-ethoxycarbonyl-2,4(1*H*,3*H*)-quinolinediones **(5d)** in 50%, 69%, and 20% yields, respectively (Scheme **A**).

Thus, the reaction products and their yields were dependent upon both amounts of base and solvent employed. As shown in Scheme **A**, these results indicate that hydrogen abstraction from the 1-position of isatoic anhydride **(1)** by sodium hydride (or the phosphonate carbanion **3**) would cause cleavage of the anhydride ring to generate a reactive intermediate isocyanate, which could subsequently react with **3** to yield the intermediate **6**, which undergoes a Wittig-Horner reaction to give the quinolinediones **5** (path A), and/or the ketenimine derivative, which undergoes cyclization to give the benzoxazine **4a** (path B).

On the other hand, the reaction of **1** with a diethyl *N*-phenylphosphoramidate anion **(7a)** in refluxing benzene for 5 h led to only 3-phenyl-2,4(1*H*,3*H*)-quinazolinedione **(8a)** in low yield, but the reaction using **2** in benzene/dimethylformamide (4:1) gave **8a** in 70% yield. Similar treatment of **2** with var-

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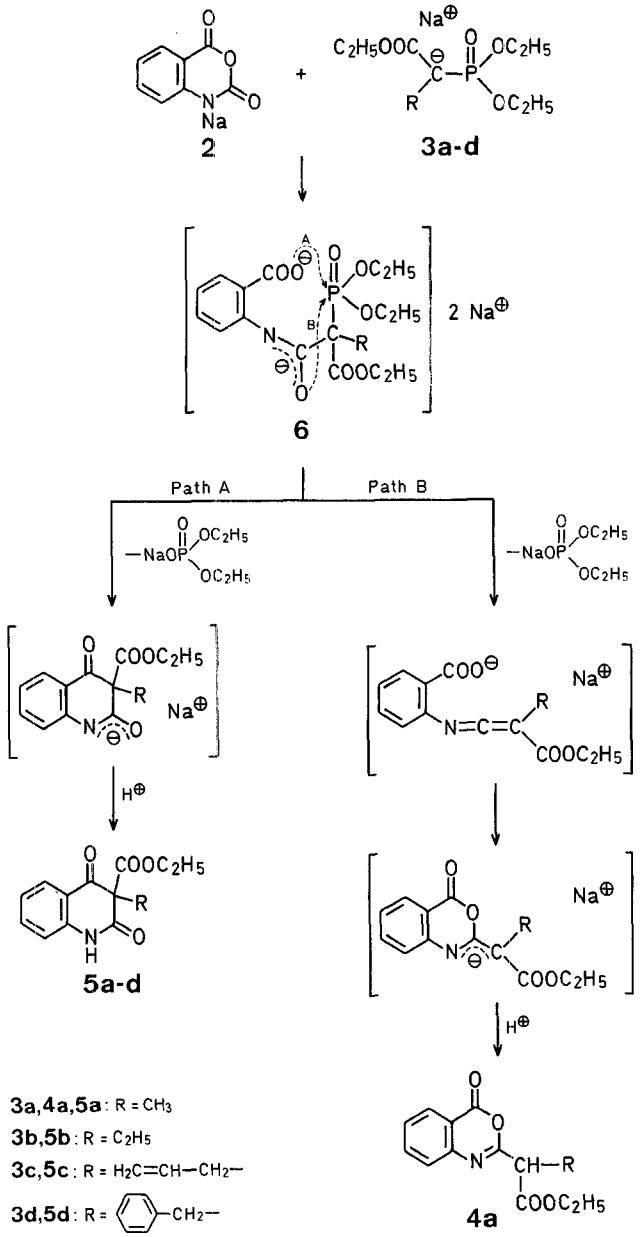
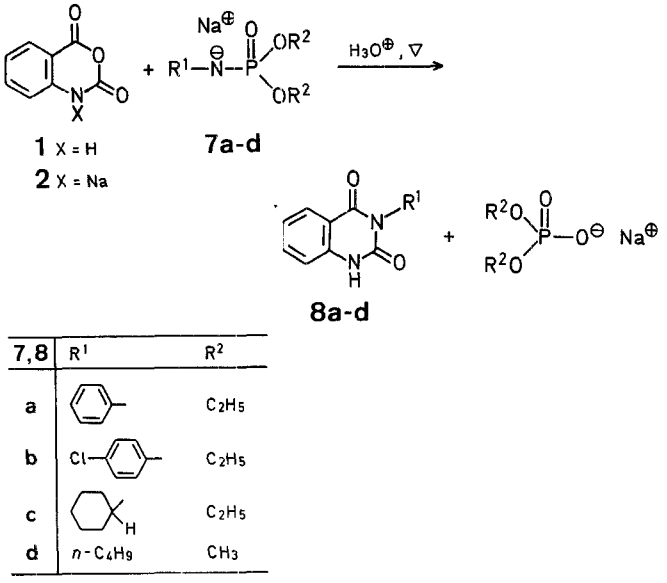


Scheme A

ious phosphoramidate anions **7b–d** in benzene/dimethylformamide provided 3-substituted-2,4(1*H*,3*H*)-quinazolinediones **8b–d** as shown in Table 1 (Scheme **B**).



7,8	R^1	R^2
a		C_2H_5
b	Cl-	C_2H_5
c	H	C_2H_5
d	n-C_4H_9	CH_3

Scheme **B**

The formation of the quinazolinediones **8** could be accounted for by a mechanism similar to that for the formation of **5**.

Thus, this method for heterocyclic compounds such as the 3,1-benzoxazin-4-one, 2,4-quinolinediones, and quinazolinediones is versatile due to its generality and simplicity, and the ease of preparation of various types of phosphoryl-stabilized anions containing no α-hydrogen atoms used as starting reagents.

All melting points were measured in open capillary tubes and are uncorrected. The N.M.R. spectra were recorded with a JEOL JNM-FX-60 or JNM-PMX-60 spectrometer with TMS as an internal standard. The I.R. spectra were obtained with a Shimazu IR-27c spectrometer. The mass spectra were recorded with a Hitachi RMU-6E spectrometer.

Ethyl 2-diethylphosphonopropanoate, b.p. 117 °C/4 torr (Lit.[7], b.p. 143–144 °C/12 torr), and *ethyl 2-diethylphosphonobutanoate*, b.p. 95 °C/1 torr (Lit.[8], b.p. 147.5–148 °C/10.5 torr) were prepared from triethyl phosphite and ethyl 2-bromopropanoate or ethyl 2-bromobutanoate. *Ethyl 2-diethylphosphono-4-pentenoate*, b.p. 105–112 °C/1.8 torr and *ethyl 2-diethylphosphono-3-phenylpropanoate*, b.p. 135–145 °C/0.1 torr were synthesized by the alkylation reaction of ethyl diethylphosphonoacetate carbanion with allyl bromide or benzyl chloride. *Diethyl N-phenyl-*, m.p. 91–92 °C (Lit.[9], m.p. 93 °C), N-p-*chlorophenyl-*, m.p. 77–78 °C (Lit.[10], m.p. 76 °C), and N-*cyclohexylphosphoramidates*, m.p. 74–75 °C (Lit.[11], m.p. 71–72 °C), and *dimethyl* N-*butylphosphorami-*

Table. 3-Substituted 2,4(1*H*,3*H*)-Quinazolinediones **8a–d** (Scheme **B**)

Product[a]	Reaction time[b] at 80 °C [h]	Yield [%]	m.p. [°C] found	m.p. [°C] reported	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]
8a	10[c]	6[c]	278–280°	280–282°[5]	7.1–8.15 (m, 9 H_{arom}); 11.63 (br s, 1 H, NH)
8a	5	70			
8b	5	99	290–291°	288°[6]	7.0–8.2 (m, 8 H_{arom}); 11.50 (br s, 1 H, NH)
8c	5	40	265–266°	270–271°[5]	0.8–2.8 (m, 10 H); 4.25–5.1 (m, 1 H); 6.8–8.05 (m, 4 H_{arom}); 11.20 (br s, 1 H, NH)
8d	10	31	154–155°	156–157°[5]	0.7–2.0 (m, 7 H); 4.10 (t, 2 H); 6.9–8.3 (m, 4 H_{arom}); 10.80 (s, 1 H, NH)

[a] Satisfactory microanalyses (C ±0.37, H ±0.15, N ±0.19) and mass spectra obtained.
[b] Reaction of **2** (15 mmol; prepared *in situ* from **1** and sodium hydride) and **7** (15 mmol) in 4:1 benzene/dimethylformamide (50 ml) unless otherwise stated.
[c] Reaction using **1** in benzene.

date, b.p. 100.5°C/1.0 torr (Lit.[12], b.p. 143°C/9 torr) were prepared from diethyl or dimethyl phosphite and the corresponding amines in the presence of carbon tetrachloride according to the established procedure[13].

Reaction of Isatoic Anhydride (1) with Ethyl 2-Diethylphosphonopropanoate Carbanion (3a):

Reaction in Benzene as Solvent: To a stirred solution of **3a** [15 mmol; generated from ethyl 2-diethylphosphonopropanoate (3.57 g, 15 mmol) and sodium hydride (15 mmol), in dry benzene (50 ml) under nitrogen] is added powdered **1** (2.45 g, 15 mmol). The reaction mixture is refluxed for 5 h and then the solvent is evaporated under reduced pressure. The residue is poured into an aqueous solution of ammonium chloride (60 ml, 0.5 molar) and extracted with ether (3 × 50 ml). The combined organic layer is dried with anhydrous sodium sulfate and concentrated. The resulting solid is chromatographed on silica gel using hexane and benzene/hexane as eluents. The first fraction gives **4a**; yield: 2.37 g (64%); m.p. 80–81°C (from hexane).

$C_{13}H_{13}NO_4$	calc.	C 63.15	H 5.30	N 5.67
(247.2)	found	63.03	5.26	5.60

M.S.: $m/e = 247$ (M^+).

I.R. (Nujol): $\nu = 1760$, 1740, 1645 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.28$ (t, 3 H, CH_3); 1.83 (d, 3 H, $>CH—CH_3$); 3.83 (q, 1 H, $>CH—CH_3$); 4.27 (q, 2 H, CH_2); 7.3–7.9 (m, 3 H_{arom}); 8.15–8.40 ppm (br d, 1 H_{arom}).

^{13}C-N.M.R. ($CDCl_3$): $\delta = 14.0$; 14.2; 46.1; 61.6; 117.2; 127.0; 128.5; 136.3; 146.3; 158.9; 160.2; 169.8 ppm.

The second fraction provides **5a**; yield: 0.15 g (4%); m.p. 147–148°C (from benzene/hexane).

$C_{13}H_{13}NO_4$	calc.	C 63.15	H 5.30	N 5.67
(247.2)	found	63.35	5.28	5.46

M.S.: $m/e = 247$ (M^+).

I.R. (Nujol): $\nu = 3200$, 1760, 1695, 1660 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.17$ (t, 3 H, CH_3); 1.83 [s, 3 H, $>C(CH_3)(COOC_2H_5)$]; 4.27 (q, 2 H, CH_2); 7.1–7.9 (m, 3 H_{arom}); 7.93–8.20 (br d, 1 H_{arom}); 10.37 ppm (br d, 1 H, NH).

^{13}C-N.M.R. ($CDCl_3$): $\delta = 13.8$; 20.8; 62.4; 63.9; 116.8; 117.8; 123.9; 128.0; 136.7; 140.9; 166.6; 171.2; 191.6 ppm.

Reaction in Benzene/Dimethylformamide as Solvent: A solution of **1** (2.45 g, 15 mmol) in dry dimethylformamide (10 ml) is added to a solution of **3a** (15 mmol) in benzene (40 ml). The reaction mixture is refluxed for 5 h. Similar treatment as described above gives a mixture of **4a**; yield: 0.67 g (18%) and **5a**; yield: 1.59 g (43%).

Reaction of *N*-Sodioisatoic Anhydride (2) with 3a in Benzene/Dimethylformamide:

A solution of **1** (2.45 g, 15 mmol) in dry dimethylformamide (10 ml) is added dropwise to a stirred solution of **3a** (15 mmol) in dry benzene (40 ml) containing sodium hydride (15 mmol). The reaction is carried out in a similar manner as above and worked up to give **5a**; yield: 2.23 g (60%).

3-Ethoxycarbonyl-3-ethyl-2,4(1*H*,3*H*)-quinolinedione (5b):

The reaction of **2** (15 mmol) with ethyl 2-diethylphosphonobutanoate carbanion (**3b**, 15 mmol) in benzene/dimethylformamide (4:1) is carried out in a similar manner as above to give the quinolinedione **5b**; yield: 1.95 g (50%); m.p. 262–263°C (from benzene).

$C_{14}H_{15}NO_4$	calc.	C 64.36	H 5.79	N 5.36
(261.6)	found	64.09	5.90	5.09

M.S.: $m/e = 261$ (M^+).

I.R. (KBr): $\nu = 3200$, 1750, 1695, 1660 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.89$ (t, 3 H, CH_3); 1.17 (t, 3 H, CH_3); 2.48 (q, 2 H, CH_2); 4.22 (q, 2 H, OCH_2); 7.0–8.1 (m, 4 H_{arom}); 10.31 ppm (br s, 1 H, NH).

^{13}C-N.M.R. ($CDCl_3$): $\delta = 8.9$; 14.0; 29.7; 62.4; 69.0; 116.7; 118.9; 123.9; 127.6; 136.6; 140.7; 166.2; 170.3; 190.3 ppm.

3-Allyl-3-ethoxycarbonyl-2,4(1*H*,3*H*)-quinolinedione (5c):

The quinolinedione **5c** is similarly obtained from the reaction of **2** (20 mmol) with ethyl 2-diethylphosphono-4-pentenoate carbanion (20 mmol) in benzene/dimethylformamide (4:1), yield: 3.77 g (69%); m.p. 121–122°C (from benzene/hexane).

$C_{15}H_{15}NO_4$	calc.	C 65.92	H 5.53	N 5.13
(273.3)	found	65.67	5.74	5.02

M.S.: $m/e = 273$ (M^+).

I.R. (KBr): $\nu = 3200$, 1760, 1700, 1660, 1620 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.16$ (t, 3 H, CH_3); 3.17 (d, 2 H, $—CH_2—CH=CH_2$); 4.21 (q, 2 H, CH_2); 4.8–6.0 (m, 3 H, $—CH_2—CH=CH_2$); 7.0–8.1 (m, 4 H_{arom}); 10.51 ppm (s, 1 H, NH).

^{13}C-N.M.R. ($CDCl_3$): $\delta = 13.8$; 40.2; 62.5; 68.0; 116.9; 118.8; 120.3; 124.0; 127.7; 130.4; 136.8; 141.1; 166.0; 170.0; 191.0 ppm.

The reaction in benzene gave no product; starting isatoic anhydride was recovered in 88% yield.

3-Benzyl-3-ethoxycarbonyl-2,4(1*H*,3*H*)-quinolinedione (5d):

The quinolinedione **5d** is similarly produced from the reaction using **2** (15 mmol) and **3d** (15 mmol) in 4:1 benzene/dimethylformamide (50 ml); yield: 0.85 g (20%); m.p. 184–184.5°C (from benzene).

$C_{19}H_{17}NO_4$	calc.	C 70.57	H 5.30	N 4.33
(323.3)	found	70.52	5.32	4.41

M.S.: $m/e = 323$ (M^+).

I.R. (KBr): $\nu = 3200$, 1750, 1695, 1660, 1610 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.14$ (t, 3 H, CH_3); 3.72 (s, 2 H, CH_2Ph); 4.20 (q, 2 H, CH_2); 6.7–7.9 (m, 10 H_{arom}); 9.84 ppm (s, 1 H, NH).

^{13}C-N.M.R. ($CDCl_3$): $\delta = 13.8$; 42.0; 62.6; 69.0; 116.5; 119.0; 123.9; 125.4; 126.0; 127.2; 127.4; 128.0; 129.7; 133.7; 136.6; 140.7; 166.1; 170.1; 191.6 ppm.

3-Phenyl-2,4(1*H*,3*H*)-quinazolinedione (8a); Typical Procedure:

To a solution containing sodium hydride (15 mmol) and the phosphoramidate anion **7a**, prepared from diethyl *N*-phenylphosphoramidate (3.44 g, 15 mmol) and sodium hydride (15 mmol), in dry benzene (40 ml) under nitrogen is added a solution of **1** (2.45 g, 15 mmol) in dry dimethylformamide (10 ml). The mixture is refluxed for 5 h. After similar work-up, the ether extract gives 3-phenyl-2,4(1*H*,3*H*)-quinazolinedione (**8a**); yield: 2.50 g (70%).

I.R. (KBr): $\nu = 3200$, 1725, 1660 cm^{-1}.

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