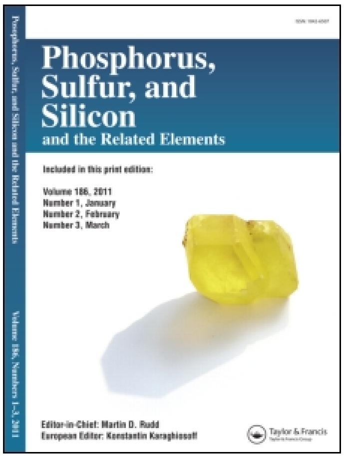

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ON THE REACTION OF 3-ACETYL COUMARIN WITH ALKYL PHOSPHITES. STRUCTURAL CONFIRMATIONS BASED ON X-RAY CRYSTALLOGRAPHY

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*3-Acetyl coumarin (**1**) reacts with dialkyl phosphites at 100°C for 8 h to give the phosphonates **2**. Under the same experimental conditions, **1** reacts with trialkyl phosphites to form a mixture of the phosphonates **2** and **3**. The molecular structures of these products were elucidated by x-ray crystallography.*

Keywords: 3-Acetyl coumarin; alkyl phosphites; x-ray crystallography

Numerous pharmacological and physiological activities have been attributed to the coumarin derivatives such as anticoagulant,[1–4] antibacterial,[5–7] potent anti-HIV,[8] molluscicidal, and anthelmintic[9–11] properties, in addition to diuretic[12–14] and respiratory stimulant[15–17] effects. From all the above findings, it has been worthy to investigate the synthesis of novel coumarin derivatives containing phosphonate residue. The present study will include the determination of the stereochemical structure of the prepared compounds.

Recently, we reported[18] that 3-acetyl coumarin (**1**) reacts with trialkyl phosphites without using solvents at 100°C for 8 h to yield a mixture of stable phosphonate derivatives **2** and **3**. The formation of compounds **2** is due to the presence of moisture during the reaction. Under the same experimental conditions, dialkyl phosphites react with **1** to form the colorless crystalline products of the phosphonates **2**, which respond positively to the ferric chloride color reaction, denoting the presence of the enol group. The phosphonates **2** and **3** are stable products and were isolated in pure form. Their assigned

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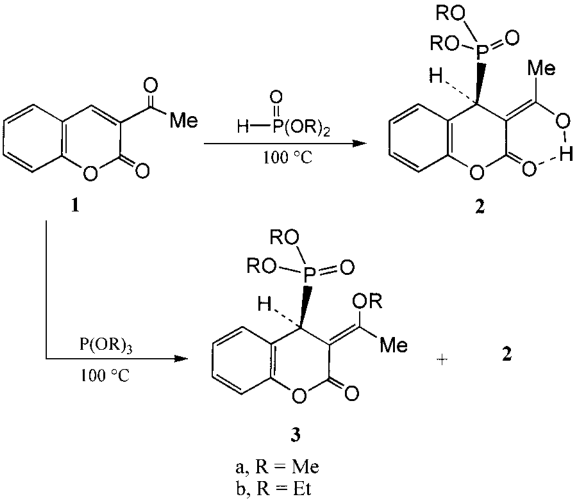
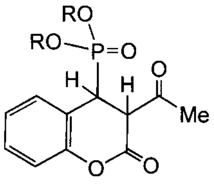
structures were verified by compatible elemental analyses, molecular weight determinations (MS), IR, ^{1}H, and ^{13}C NMR spectra.[18] After publishing our work, Abdou and Sediek[19] reported that the reaction of 3-acetyl coumarin (**1**) with dialkyl phosphites in the absence



of solvents gives the phosphonate adducts **2** with the tautomers **4** (in ratio 1:3), which exist in equilibrium **2** ⇌ **4**, and they could not isolate any of the described product in pure form despite of clarification cited in our previous article[18] that we have isolated the stable compounds **2** (85% yield) in pure form as sole products, with complete



4 a, R = Me
b, R = Et

confirmed spectroscopic data. In other words, through the previously described spectroscopic data as well as the stablished single crystal x-ray structure analysis (Figure 1), it could be concluded that the enol form for the assigned structure **2** is more predominant than

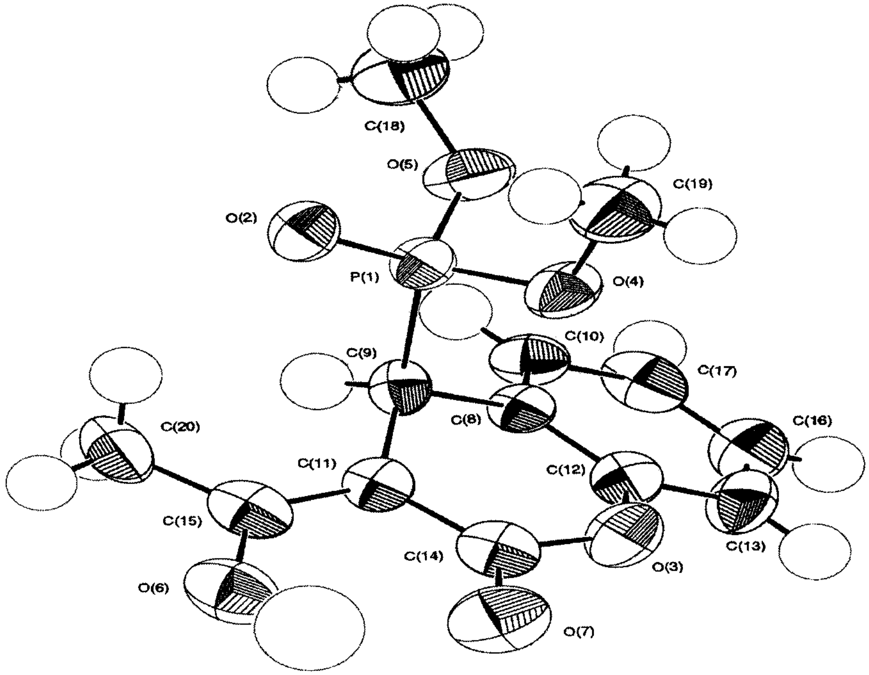
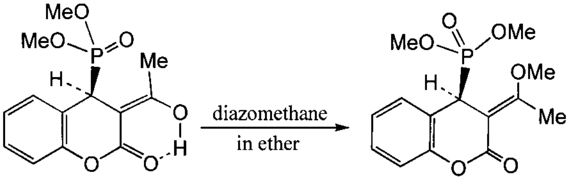


FIGURE 1 Molecular structure of $C_{13}H_{15}O_6P$, **2a**. Selected bond lengths (Å) and angles (°): P(1)–O(2) 1.4598(5), P(1)–O(4) 1.5753(6), P(1)–O(5) 1.5605(6), P(1)–C(9) 1.8138(7), O(4)–C(19) 1.4377(10), O(5)–C(18) 1.4157(10), O(6)–C(15) 1.3336(10), O(7)–C(14) 1.2203(9), C(9)–C(11) 1.5097(10), C(11)–C(14) 1.4409(11), C(11)–C(15) 1.3609(11), C(15)–C(20) 1.4837(12), O(6)–H(6) 0.870(11), O(7)–H(6) 1.823(12), C(9)–H(9) 0.9600(7), O(2)–P(1)–O(4) 114.51(3), O(2)–P(1)–O(5) 114.23(3), O(2)–P(1)–C(9) 115.83(4), O(4)–P(1)–O(5) 103.65(3), O(4)–P(1)–C(9) 101.31(3), O(5)–P(1)–C(9) 105.76(3), P(1)–O(5)–C(18) 124.26(6), P(1)–C(9)–C(8) 112.31(5), P(1)–C(9)–C(11) 111.43(5), C(9)–C(11)–C(15) 122.28(8), C(14)–C(11)–C(15) 118.60(8), O(7)–C(14)–C(11) 125.58(9), O(6)–C(15)–C(11) 122.37(9), C(11)–C(15)–C(20) 125.23(9), C(15)–O(6)–H(6) 111.6(8), P(1)–C(9)–H(9) 109.48(6), C(8)–C(9)–H(9) 106.17(6), C(11)–C(9)–H(9) 106.60(7).

the keto form **4** where no evidence has been observed for the latter structure.

Single crystal x-ray analysis of **2a** (Figure 1) confirms not only the stereochemical configuration of the isolated product but also explain the hydrogen bonding located between the lactonic carbonyl and the adjacent hydroxyl group [O(7)—H(6) bond length 1.823 (12) Å]. This measurement supports the previous report,[18] based on the IR and NMR (^1H, ^{13}C) spectral data. Moreover, the bond lengths 1.3609(11), 1.3568(9), 1.3433(9) Å of the exocyclic C=C of the corresponding products **2a**, **3a**, **3′a** are in good agreement values with the established structures.

In our previous article,[18] we reported that the phosphonate **2a** reacts with an ethereal solution of diazomethane at room temperature to give a product identical in all respects [m.p. and mixed m.p. (180–181°C), comparative IR and ^{1}H NMR spectra] with the phosphonate **3a**, produced from the reaction of 3-acetyl coumarin (**1**) with trimethyl phosphite at 100°C.



2a **3'a**

The ORTEP perspective view of the single crystal x-ray structure of **3a** (Figure 2) compared with the product **3′a** (Figure 3), obtained from the reaction of the phosphonate **2a** with diazomethane supports this assumption and also, exhibits the stereochemical configuration of the products which could be explained in terms of free rotation of phosphonate function around the single bond. Formation of **3′a** through diazomethane alkylation of **2a** could be attributed due to keto-enol isomerism taking place during alkylation process under the applied reaction conditions. Single crystal x-ray of **3′a** (Figure 3) shows this presumption exhibiting the pure assigned geometrical stereochemical isomer.

In conclusion, single crystal x-ray analysis has supported beyond any doubt our previous results[18] and confirmed the solid state structures of the phosphonates **2a**, **3a**, and **3′a** results.

X-RAY STRUCTURE DETERMINATIONS

The crystal data were measured at $T = 298$ K on KappaCCD Enraf Nonius FR 590 diffractometer. The crystal structures were solved and refined using maXus (Nonius, Delft and MacScience, Japan). Mo-Kα radiation ($\lambda = 0.71073$ Å) and a graphite monochromator were used for data collection.

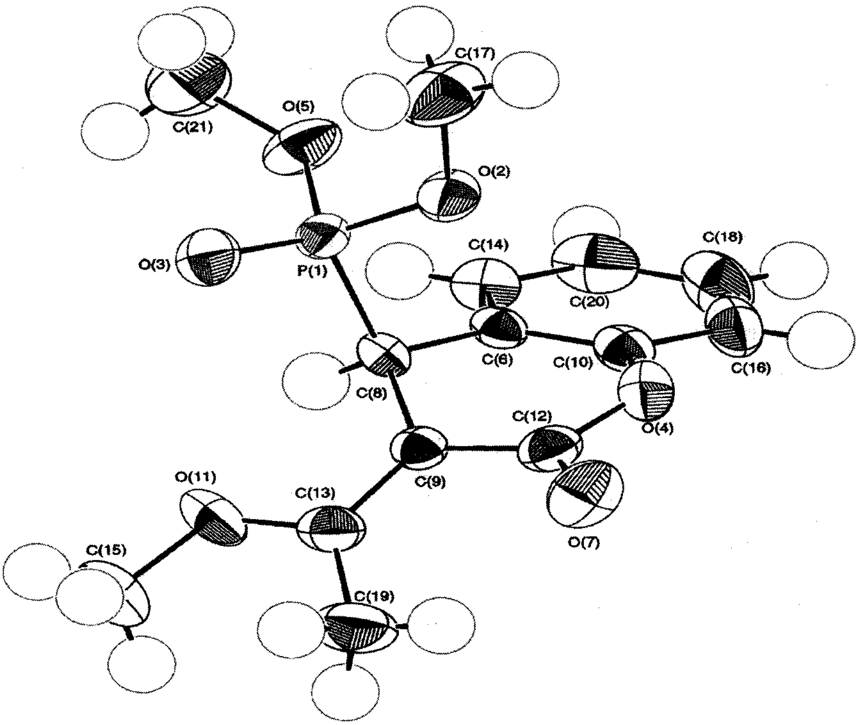


FIGURE 2 Molecular structure of $C_{14}H_{17}O_6P$, **3a**. Selected bond lengths (Å) and angles (°): P(1)–O(3) 1.4542(4), P(1)–O(2) 1.5709(5), P(1)–O(5) 1.5558(5), P(1)–C(8) 1.8079(7), O(5)–C(21) 1.3994(9), O(11)–C(13) 1.3523(8), O(7)–C(12) 1.2033(7), C(8)–C(9) 1.5136(8), C(9)–C(12) 1.4617(9), C(9)–C(13) 1.3568(9), C(13)–C(19) 1.4892(10), O(11)–C(15) 1.4028(9), C(8)–H(8) 0.9600(6), O(3)–P(1)–O(2) 115.62(3), O(3)–P(1)–O(5) 114.49(3), O(3)–P(1)–C(8) 115.00(3), O(2)–P(1)–O(5) 103.78(3), O(2)–P(1)–C(8) 102.00(3), O(5)–P(1)–C(8) 104.35(3), P(1)–O(5)–C(21) 125.77(5), P(1)–C(8)–C(6) 113.39(5), P(1)–C(8)–C(9) 111.37(4), C(8)–C(9)–C(13) 120.28(6), C(12)–C(9)–C(13) 121.56(6), O(7)–C(12)–C(9) 127.78(7), O(11)–C(13)–C(9) 118.68(7), C(9)–C(13)–C(19) 126.19(7), C(13)–O(11)–C(15) 121.93(7), P(1)–C(8)–H(8) 108.53(5), C(6)–C(8)–H(8) 105.58(5), C(9)–C(8)–H(8) 107.37(6).

Phosphonate 2a

$C_{13}H_{15}O_6P$, $M_r = 298.281$, monoclinic, crystallizes in space group $P2_1/c$, $a = 15.551(2)$, $b = 6.9437(6)$, $c = 24.587(2)$ Å, $V = 1375.3(2)$ Å^3, $Z = 4$, $D_c = 1.44$ g cm^{-3}, 2θ range 2.91–27.48°, absorption coefficient μ (Mo-Kα) = 0.22 mm^{-1}, $F(000) = 624$. The unique reflections measured 2914, of which 1747 reflections with threshold expression $I > 3\sigma(I)$

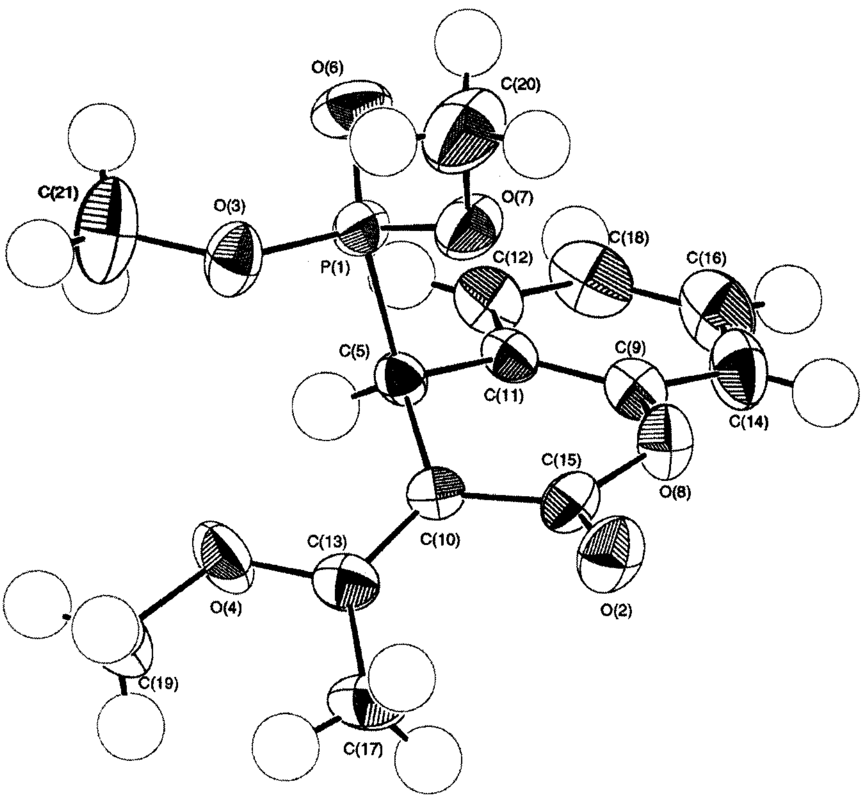


FIGURE 3 Molecular structure of $C_{14}H_{17}O_6P$, **3′a**. Selected bond lengths (Å) and angles (°): P(1)–O(6) 1.4592(5), P(1)–O(7) 1.5688(5), P(1)–O(3) 1.5805(5), P(1)–C(5) 1.8139(6), O(3)–C(21) 1.4220(10), O(4)–C(13) 1.3617(8), O(2)–C(15) 1.2079(8), C(5)–C(10) 1.5135(8), C(10)–C(15) 1.4557(9), C(10)–C(13) 1.3433(9), C(13)–C(17) 1.4803(10), O(4)–C(19) 1.4169(9), C(5)–H(5) 0.9600(6), O(6)–P(1)–O(7) 116.49(3), O(3)–P(1)–O(6) 114.35(3), O(6)–P(1)–C(5) 114.43(3), O(3)–P(1)–O(7) 101.70(3), O(7)–P(1)–C(5) 101.87(3), O(3)–P(1)–C(5) 106.40(3), P(1)–O(3)–C(21) 120.63(5), P(1)–C(5)–C(11) 111.15(4), P(1)–C(5)–C(10) 113.08(4), C(5)–C(10)–C(13) 121.49(6), C(13)–C(10)–C(15) 121.12(6), O(2)–C(15)–(10) 128.13(7), O(4)–C(13)–C(10) 114.29(6), C(10)–C(13)–C(17) 127.35(7), C(13)–O(4)–C(19) 121.30(6), P(1)–C(5)–H(5) 108.76(4), C(11)–C(5)–H(5) 107.11(5), C(10)–C(5)–H(5) 106.33(5).

were used in the structural analysis. Convergence for 185 variable parameters by least-squares refinement on F^2 with $w = 1/[\sigma^2(F_o^2) + 0.03F_o^2]$. The final agreement factors were $R = 0.064$ and $wR = 0.093$ with a goodness-of-fit of 1.601.

Phosphonate 3a

$C_{14}H_{17}O_6P$, $M_r = 312.258$, monoclinic, crystallizes in space group $P2_1/c, a = 7.1031(3), b = 26.185(2), c = 8.6298(5)$ Å, $V = 1485.59(14)$ Å^3, $Z = 4, D_c = 1.396$ g cm^{-3}, 2θ range 2.91–27.48°, absorption coefficient μ (Mo-Kα) $= 0.21$ mm^{-1}, $F(000) = 656$. The unique reflections measured 3227, of which 1991 reflections with threshold expression $I > 3\sigma(I)$ were used in the structural analysis. Convergence for 190 variable parameters by least-squares refinement on F^2 with $w = 1/[\sigma^2(F_o^2) + 0.03F_o^2]$. The final agreement factors were $R = 0.055$ and $wR = 0.061$ with a goodness-of-fit of 1.702.

Phosphonate 3′a

$C_{14}H_{17}O_6P$, $M_r = 312.258$, monoclinic, crystallizes in space group $C\ c$, $a = 7.8227(6), b = 15.3091(11), c = 12.5233(9)$ Å, $V = 1491.3(2)$ Å^3, $Z = 4, D_c = 1.391$ g cm^{-3}, 2θ range 2.91–27.48°, absorption coefficient μ (Mo-Kα) $= 0.21$ mm^{-1}, $F(000) = 656$. The unique reflections measured 1693, of which 1493 reflections with threshold expression $I > 3\sigma(I)$ were used in the structural analysis. Convergence for 188 variable parameters by least-squares refinement on F^2 with $w = 1/[\sigma^2(F_o^2) + 0.03F_o^2]$. The final agreement factors were $R = 0.041$ and $wR = 0.056$ with a goodness-of-fit of 1.565.

Further details of the structure determination (complete bond lengths and angles, H atom coordinates, structure factors, temperature factors) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, United Kingdom. Any request should be accompanied by the full literature citation and the CCDC reference numbers 178481 **(2a)**, 178482 **(3a)**, and 178483 **(3′a)**.

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