

The Behavior of 3,3-Diphenylindan-1,2-dione Towards Alkyl Phosphites

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Received April 10, 2007; accepted (revised) April 13, 2007; published online July 20, 2007

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Summary. The reaction of 3,3-diphenylindan-1,2-dione with trimethyl phosphite in dry benzene at room temperature for about 15 h led to the formation of a mixture containing dimethyl (3,3-diphenyl-2-methoxy-1-indenyl)phosphate and dimethyl (3,3-diphenyl-1*H*-2-oxo-1-indanyl)phosphate, whereas with triisopropyl phosphite, diisopropyl (3,3-diphenyl-2-isopropoxy-1-indenyl)phosphate is the only product. Treatment of the dione with dialkyl phosphites under different experimental conditions gave dialkyl (3,3-diphenyl-1-hydroxy-2-oxo-1-indanyl)phosphates. Reaction mechanisms are presented which account for the experimental results. Structural assignments of the new compounds are based on the spectroscopic evidences and two examples were elucidated by X-ray crystallography.

Keywords. 3,3-Diphenylindan-1,2-dione; Alkyl phosphites; X-Ray crystallography.

Introduction

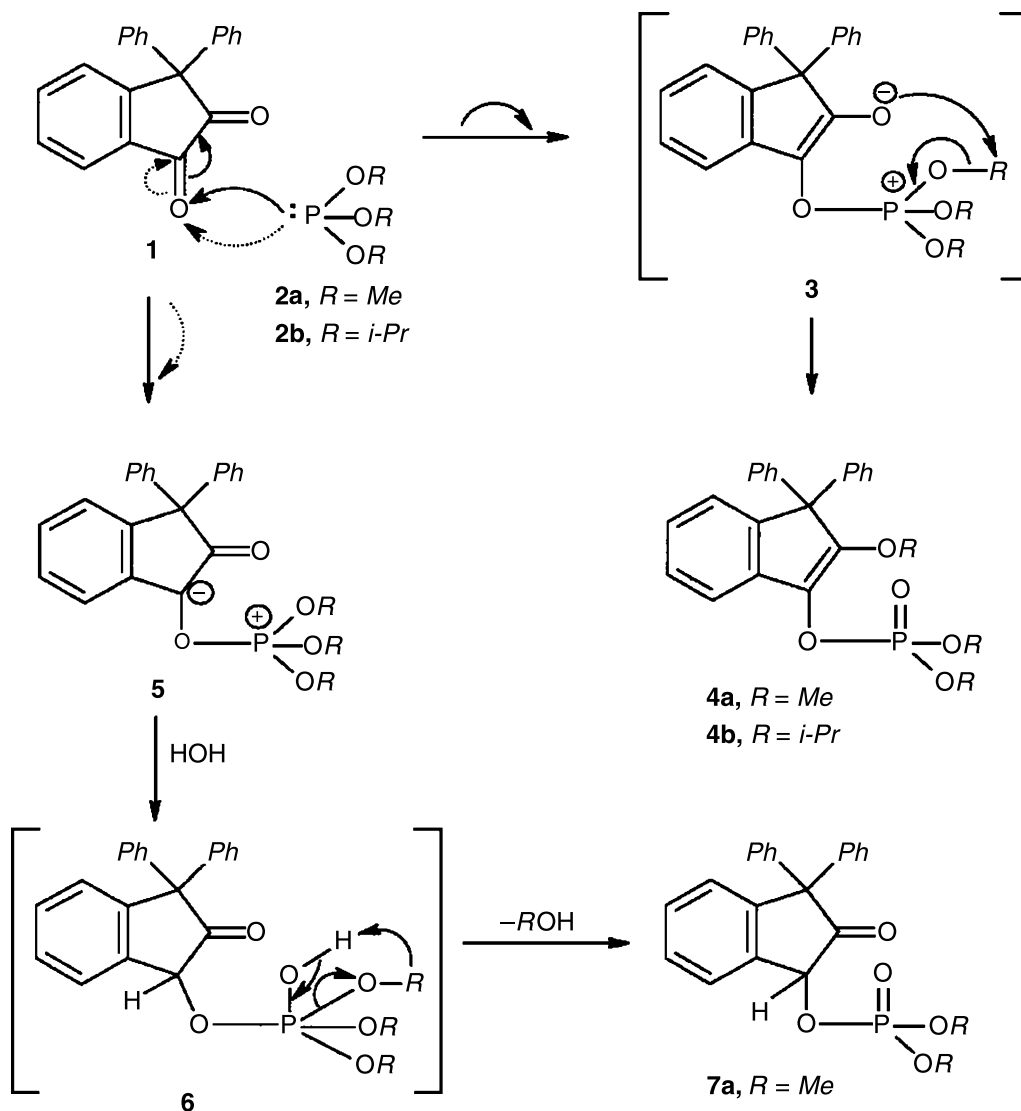
The reaction of phosphite esters with *o*-quinones and α -diketones has been extensively studied by several investigators [1–26]. It has been found that the course of the reaction depends on the nature of the carbonyl compounds. Thus, trialkyl phosphites react with α -dicarbonyl compounds, such as biacetyl [27, 28], phenanthrenequinone [27], *o*-chloranil [29], and 4-triphenylmethyl-1,2-benzoquinone [23], to form 1:1 adducts of cyclic unsaturated pentaoxyphosphoranes whereas, with acenaphenequinone [30, 31], isatin [32, 33], and 5,6-dihydrocyclopent[*fg*]acenaphthylene-1,2-dione [34] they give 1:2 adducts constituting

cyclic saturated pentaoxyphosphoranes. In some cases, other types of α -diketones undergo alkylation *via* alkyl group translocation to afford the phosphate or the phosphonate esters [18, 20, 29, 35, 36]. Dialkyl phosphites react with α -dicarbonyl compounds to form 1:1 adducts of α -hydroxyphosphonates or *o*-quinol monophosphates [24–26, 29, 32, 34, 36–46]. From the course of these studies and in continuation with our previous paper [47], it seemed to be of interest to examine the reactivity of 3,3-diphenyl-1,2-dione as an asymmetrical α -diketone with alkyl phosphites.

Results and Discussion

We found that 3,3-diphenylindan-1,2-dione (**1**) reacted with trimethyl phosphite (**2a**) in dry benzene at room temperature to give a mixture of dimethyl (3,3-diphenyl-2-methoxy-1-indenyl)phosphate (**4a**) and dimethyl (3,3-diphenyl-1*H*-2-oxo-indanyl)phosphate (**7a**) (Scheme 1). These products were separated by column chromatography on silica gel as colorless crystalline products and their structures were established by different spectroscopic techniques as well as elemental analyses and molecular weight determination (MS). The IR spectrum of the phosphate **4a** reveals the absence of a carbonyl absorption band around 1700 cm^{-1} . In addition, it exhibits intense bands at 1270 and 1065 cm^{-1} corresponding to P=O and P–O–*Me* stretching vibrations [48]. Its ^1H NMR exhibits a doublet at $\delta = 3.84$ with $J_{\text{HP}} = 11.10\text{ Hz}$ due to the two methoxy groups

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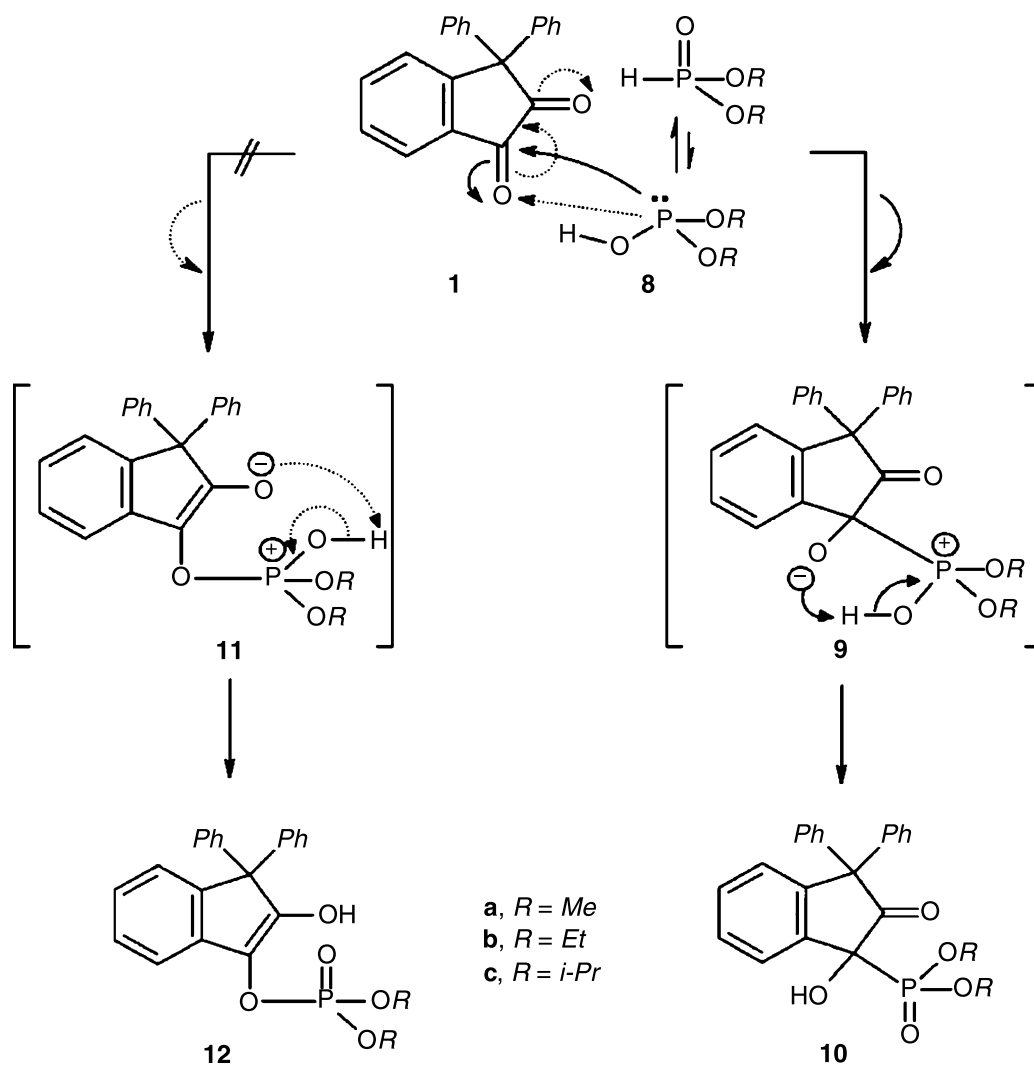


Scheme 1

attached to phosphorus [48]. It also shows a signal at $\delta = 3.98$ for the methoxy group at C-2. Moreover, a single crystal X-ray diffraction analysis of **4a** (Fig. 1) confirms the established configuration. The other product **7a** shows characteristic bands in the IR spectrum at 1753 cm^{-1} for the carbonyl group and at 1235 and 1056 cm^{-1} due to the absorption of the P=O and P-O-Me groups. Its ^1H NMR disclosed the presence of two doublets at $\delta = 3.56, 3.87$ ppm with $J_{\text{HP}} = 11.10$ Hz ascribed to the two methoxy groups attached to the phosphorus atom. The presence of a doublet at $\delta = 5.81$ ppm with $J_{\text{HP}} = 10.5$ Hz for the proton at C-1 is also good evidence supporting structure **7a**.

A possible explanation for the course of the reaction of trimethyl phosphite (**2a**) with 3,3-diphe-

nylindan-1,2-dione (**1**) is shown in Scheme 1. The reaction goes on two pathways to form the products **4a** and **7a**. The first pathway involves a nucleophilic attack by the phosphite-phosphorus on the carbonyl oxygen at position 1 in dione **1** to form the intermediate dipolar adduct **3a**, which then undergoes group translocation with formation of the ether phosphate ester **4a**. The second pathway is initiated by nucleophilic addition of the phosphite-phosphorus on the most reactive carbonyl at C-1 of the dione **1** to give the phosphonium species **5a**, which in presence of unavoidable moisture can add water to furnish a transient intermediate **6a** with pentavalent phosphorus followed by ejection of one mole of methanol to give the product **7a**.



Scheme 2

Triisopropyl phosphite (**2b**) reacted with dione **1** in benzene solution to give as the sole product diisopropyl (3,3-diphenyl-2-isopropoxy-1-indenyl)phosphate (**4b**) as colorless crystals. Its structure was confirmed by elemental analyses, IR, ^1H NMR, and MS (*cf.* Experimental).

The reaction of dione **1** with dialkyl phosphites (**2a–2c**) in benzene solution or in absence of solvents gave colorless crystalline products of dialkyl (3,3-diphenyl-1-hydroxy-2-oxo-1-indanyl)phosphonates **10** and not the enol-phosphate esters **12** (Scheme 2). Similar results were obtained when the reactants in benzene solution were catalyzed by direct sunlight (photolysis) at ambient temperature. The assignment of structure **10** was based on the correct analytical values, IR, ^1H NMR, and molecular weight determination (MS). The IR spectra of the

phosphonates **10a–10c** showed the characteristic absorption band at 3150 cm^{-1} attributable to the stretching frequency of an OH function. They exhibit intense bands at 1230 cm^{-1} corresponding to the P=O and at 1050 cm^{-1} for P–O–C (alkyl) stretching vibration. Also, they show a strong absorption band at 1750 cm^{-1} due to the carbonyl group. The ^1H NMR spectrum of **10a**, taken as an example, is consistent with the α -hydroxyphosphonate structure. It disclosed the two anisotropic methoxy groups attached to phosphorus appearing as two doublets (each with $J_{\text{HP}} = 10.8\text{ Hz}$) at $\delta = 3.39, 3.98\text{ ppm}$. The anisotropy is expected to be induced by the chiral carbon bearing the phosphorus atom. A singlet at $\delta = 2.52\text{ ppm}$ exchangeable with D_2O appears for the OH proton. Further evidence supporting structure **10a** is the single crystal X-ray diffraction analysis (Fig. 2).

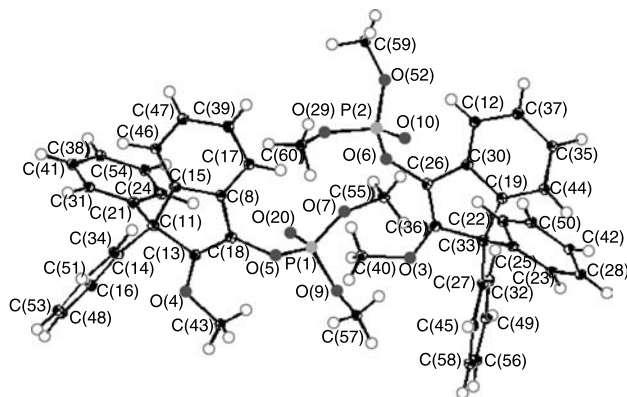


Fig. 1. ORTEP perspective view of **4a**

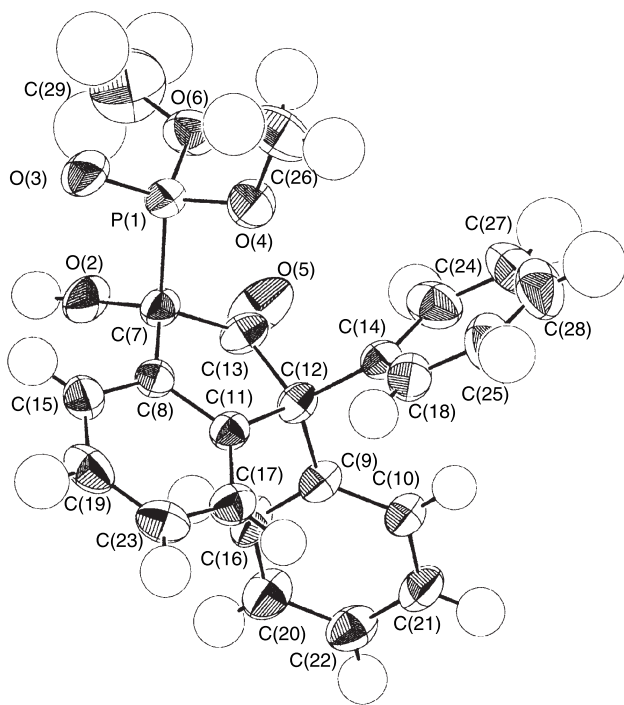


Fig. 2. ORTEP perspective view of **10a**

A mechanism that accounts for the formation of compounds **10** from the reaction of dione **1** with dialkyl phosphites **8** is depicted in Scheme 2. This involves initial nucleophilic addition of the phosphite-phosphorus to the more reactive carbon atom in position 1 to yield the phosphonium intermediate **9**, which affords the final α -hydroxyphosphonates **10**.

Conclusion

From the results obtained above it is shown that the reaction of 3,3-diphenylindan-1,2-dione (**1**) as an

asymmetrical α -diketone with trimethyl phosphite (**2a**) gave a mixture of the phosphate esters **4a** and **7a**, whereas with triisopropyl phosphite (**2b**), compound **4b** is the only product. Dialkyl phosphites **8** reacted with dione **1** under different experimental conditions to afford the α -hydroxyphosphonates **10**. This means that in dione **1** the carbonyl group at C-1 is more reactive than the one at C-2, which is sterically hindered by the adjacent phenyl groups.

Experimental

Melting points were determined on an Electrothermal digital-melting-point apparatus. Trialkyl phosphites [49, 50] were purified by prolonged treatment with sodium ribbon, followed by fractional distillation. Dialkyl phosphites [51, 52] were freshly distilled. The IR spectra were recorded in KBr disks on a Jasco Fourier Transform Infrared spectrophotometer model FT/IR-3000E. The ^1H NMR spectra were recorded in deuterated chloroform (CDCl_3) on a Varian Mercury VX-300 spectrometer (300 MHz), using tetramethylsilane (*TMS*) as an internal reference. Mass spectra (EI-MS) were determined at 70 eV on a Finnigan MAT SSQ 7000 spectrometer. 3,3-Diphenylindan-1,2-dione was prepared according to the previously reported method [53].

X-Ray Structure Determination

The crystal data were measured at $T=298$ K on a Kappa CCD Enraf Nonius FR 590 diffractometer. The crystal structure was solved and refined using maXus (Nonius, Delft and MacScience, Japan). Mo- K_α radiation ($\lambda = 0.71073$ Å) and a graphite monochromator were used for data collection. Further details of the structure determination (complete bond lengths and angles, H atom coordinates, structure factors, temperature factors) were 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 643748 (**4a**) and 643749 (**10a**).

Reaction of 3,3-Diphenylindan-1,2-dione (**1**) with Trimethyl Phosphite (**2a**)

A mixture of 0.6 g **1** (2 mmol) and 3 cm³ **2a** in 20 cm³ dry benzene was stirred at room temperature for about 15 h. Then, the volatile materials were evaporated under reduced pressure and the residue was chromatographed on silica gel using petroleum ether (bp 60–80°C) and acetone as eluent to give the two products **4a** and **7a**.

Dimethyl (3,3-diphenyl-2-methoxy-1-indenyl)phosphate (**4a**, $\text{C}_{24}\text{H}_{23}\text{O}_5\text{P}$)

Yield 48%; colorless crystals, mp 143–144°C (benzene/*n*-hexane); IR: $\bar{\nu} = 1651$ cm⁻¹ (C=C), 1270 (P=O), 1065 (P–O–C) cm⁻¹; ^1H NMR (CDCl_3): $\delta = 3.84$ [d, $J_{\text{HP}} = 11.10$ Hz, $\text{P}(\text{OCH}_3)_2$], 3.98 (s, C–OCH₃), 7.09–7.38 (m, 14ArH) ppm; MS: m/z (%) = 422 (M^+ , 91).

Crystallographic Data of 4a

$C_{24}H_{23}O_5P$, $M_r = 422.417$, orthorhombic, crystallizes in space group $Pca2_1$, $a = 16.2867(2)$, $b = 8.68360(10)$, $c = 30.4146(5)$ Å, $V = 4301.45(10)$ Å³, $Z = 8$, $D_c = 1.305$ g cm⁻³, $\theta = 2.910$ – 24.407° , absorption coefficient $\mu(\text{Mo-K}\alpha) = 0.16$ mm⁻¹, $F(000) = 1776$. The unique reflections measured 2908, of which 2172 reflections with threshold expression $I > 3\sigma(I)$ were used in the structural analysis. Convergence for 541 variable parameters by least-squares refinement on F^2 with $\omega = 1/[\sigma^2(F_0^2) + 0.10000F_0^2]$. The final agreement factors were $R = 0.043$ and $wR = 0.084$ with a goodness-of-fit of 2.043.

*Dimethyl (3,3-diphenyl-1H-2-oxo-1-indanyl)phosphate***(7a, C₂₃H₂₁O₅P)**

Yield 25%; colorless crystals, mp 108–109°C (dichloromethane/*n*-hexane); IR: $\bar{\nu} = 1753$ (C=O), 1235 (P=O), 1056 (P–O–C) cm⁻¹; ¹H NMR (CDCl₃): $\delta = 3.56, 3.87$ [2d, $J_{\text{HP}} = 11.10$ Hz, P(OCH₃)₂], 5.81 (d, $J_{\text{HP}} = 10.5$ Hz, CH–O–P), 6.90–7.86 (m, 14ArH) ppm; MS: m/z (%) = 408 (M⁺, 21).

Reaction of 3,3-Diphenylindan-1,2-dione (1) with Triisopropyl Phosphite (2b)

A mixture of 0.6 g **1** (2 mmol) and 2 cm³ **2b** in 20 cm³ dry benzene was stirred at room temperature for about 10 h and the mixture was worked up according to the described procedure for the phosphite **2a**. The chromatographic separation on silica gel using *n*-hexane/acetone as eluent gave the only product **4b**.

*Diisopropyl (3,3-diphenyl-2-isopropyl-1-indenyl)phosphate***(4b, C₃₀H₃₅O₅P)**

Yield 62%; colorless crystals, mp 96–97°C (chloroform/*n*-hexane); IR: $\bar{\nu} = 1645$ (C=C), 1271 (P=O), 1014 (P–O–C) cm⁻¹; ¹H NMR (CDCl₃): $\delta = 0.97$ [d, $J = 6.3$ Hz, 6H, C–OCH(CH₃)₂], 1.24, 1.36 {2d, $J = 6.3$ Hz, 12H, P[OCH(CH₃)₂]₂}, 4.75, 4.77 {2 quintets, $J = 6.3$ Hz, 2H, P[OCH(CH₃)₂]₂}, 5.08 [quintet, $J = 6.0$ Hz, 1H, C–OCH(CH₃)₂], 7.03–7.45 (m, 14ArH) ppm; MS: m/z (%) = 506 (M⁺, 10).

*Reaction of 3,3-Diphenylindan-1,2-dione (1) with Dialkyl Phosphites (8a–8c), General Procedures**a) In Absence of Solvent*

A mixture of 0.6 g **1** (2 mmol) was dissolved in 3 cm³ of the appropriate dialkyl phosphites (**8**) at 40°C. Then, the solution was left at room temperature. After about two weeks, 10 cm³ mixture of benzene/petroleum ether (bp 60–80°C) (1:5) was added and the solution was left in the ice-chest overnight. The colorless crystals, thus formed, were filtered off and recrystallized from a suitable solvent to give the α -hydroxyphosphonates **10a–10c**.

b) In Presence of Solvent

A mixture of 0.6 g **1** (2 mmol) and 2 cm³ **8** in 20 cm³ dry benzene was heated under reflux on a steam bath at 70°C for about 40 h. Then, the solution was concentrated under reduced pressure, followed by dropwise addition of petroleum ether (bp 60–80°C), upon which the colorless crystals

were precipitated. It was filtered off and proved to be the α -hydroxyphosphonates **10a–10c**.

c) Photochemical Reaction

To a solution of 0.6 g **1** (2 mmol) in 15 cm³ dry benzene, 2 cm³ **8** were added. The mixture was exposed to sunlight for 10 days (June). At the end of the experiment, the dione **1** was changed into colorless crystals, filtered off, and proven to be the α -hydroxyphosphonates **10a–10c**. The filtrate was evaporated under reduced pressure and the residue was treated with benzene/petroleum ether (bp 60–80°C) to give an additional amount of the colorless products **10a–10c**.

*Dimethyl (3,3-diphenyl-1-hydroxy-2-oxo-1-indanyl)**phosphonate (10a, C₂₃H₂₁O₅P)*

Yield 76%; colorless crystals, mp 175–176°C (chloroform/*n*-hexane); IR: $\bar{\nu} = 3161$ (OH), 1757 (C=O), 1234 (P=O), 1055 (P–O–C) cm⁻¹; ¹H NMR (CDCl₃): $\delta = 2.52$ (s, OH), 3.39, 3.98 [2d, $J_{\text{HP}} = 10.8$ Hz, P(OCH₃)₂], 6.80–7.83 (m, 14ArH) ppm; MS: m/z (%) = 408 (M⁺, 3).

Crystallographic Data of 10a

$C_{23}H_{21}O_5P$, $M_r = 408.390$, monoclinic, crystallizes in space group $P2_1/c$, $a = 15.2201(3)$, $b = 8.9602(2)$, $c = 17.7349(7)$ Å, $V = 2064.94(10)$ Å³, $Z = 4$, $D_c = 1.314$ g cm⁻³, $\theta = 2.910$ – 27.485° , absorption coefficient $\mu(\text{Mo-K}\alpha) = 0.16$ mm⁻¹, $F(000) = 856$. The unique reflections measured 5324, of which 2491 reflections with threshold expression $I > 3\sigma(I)$ were used in the structural analysis. Convergence for 262 variable parameters by least-squares refinement on F^2 with $\omega = 1/[\sigma^2(F_0^2) + 0.10000F_0^2]$. The final agreement factors were $R = 0.048$ and $wR = 0.091$ with a goodness-of-fit of 1.780.

*Diethyl (3,3-diphenyl-1-hydroxy-2-oxo-1-indanyl)**phosphonate (10b, C₂₅H₂₅O₅P)*

Yield 74%; colorless crystals, mp 184–185°C [benzene/petroleum ether (bp 60–80°C)]; IR: $\bar{\nu} = 3157$ (OH), 1757 (C=O), 1230 (P=O), 1051 (P–O–C) cm⁻¹; ¹H NMR (CDCl₃): $\delta = 1.04, 1.06$ [2t, $J = 7.0$ Hz, 6H, P(OCH₂CH₃)₂], 3.12 (broad s, OH), 3.65–3.99 [m, 4H, P(OCH₂CH₃)₂], 6.84–7.82 (m, 14 ArH) ppm; MS: m/z (%) = 436 (M⁺, 8).

*Diisopropyl (3,3-diphenyl-1-hydroxy-2-oxo-1-indanyl)**phosphonate (10c, C₂₇H₂₉O₅P)*

Yield 71%; colorless crystals, mp 181–182°C (chloroform/*n*-hexane); IR: $\bar{\nu} = 3134$ (OH); 1757 (C=O), 1226 (P=O), 1047 (P–O–C) cm⁻¹; ¹H NMR (CDCl₃): $\delta = 1.01, 1.02, 1.09, 1.10$ {4d, $J = 6.3$ Hz, 12H, P[OCH(CH₃)₂]₂}, 2.82 (broad s, OH), 4.50–4.67 {m, 2H, P[OCH(CH₃)₂]₂}, 6.83–7.82 (m, 14ArH) ppm; MS: m/z (%) = 464 (M⁺, 100).

References

- [1] Osman FH, El-Samahy FA (2002) Chem Rev **102**: 629
- [2] Ramirez F (1964) Pure Applied Chem **9**: 337
- [3] Ramirez F (1966) Bull Soc Chim Fr 2443

- [4] Konovalova IV, Pudovik AN (1972) *Russ Chem Rev* **41**: 411
- [5] Kukhtin VA, Kirillova KM (1962) *J Gen Chem USSR* **32**: 2755
- [6] Ramirez F, Kügler H (1973) *Phosphorus* **2**: 203
- [7] Birum GH, Dever JL (1961) US Patent 3,014,949; (1962) *Chem Abstr* **56**: 10190i
- [8] Stephenson LM, Falk LC (1976) *J Org Chem* **41**: 2928
- [9] Ogata Y, Yamashita M (1970) *J Am Chem Soc* **92**: 4670
- [10] Kirillova KM, Kukhtin VA (1965) *Zh Obshch Khim* **35**: 544; *Chem Abstr* **63**: 523c
- [11] Levin YaA, Gozman IP, Salikhov SG (1968) *Izv Akad Nauk SSSR Ser Khim* 2609; (1969) *Chem Abstr* **70**: 68269v
- [12] Mizrakh LI, Sandalova LYu, Evdakov VP (1968) *Zh Obshch Khim* **38**: 1107; *Chem Abstr* **69**: 77367g
- [13] Koole LH, Lanters EJ, Buck HM (1984) *J Am Chem Soc* **106**: 5451
- [14] De Keijzer AEH, Buck HM (1988) *J Org Chem* **53**: 4827
- [15] Van Genderen MHP, Koole LH, Olde Sheper BCCM, Van de Ven LJM, Buck HM (1987) *Phosphorus Sulfur* **32**: 73
- [16] Koole LH, Van Genderen MHP, Buck HM (1988) *J Org Chem* **53**: 5266
- [17] Zhao Y-F, Zhou Y-S (2000) *Synthetic Commun* **30**: 2769
- [18] Wiley DW, Simmons HE (1964) *J Org Chem* **29**: 1876
- [19] Kinney WA, Abou-Gharbia M, Garrison DT, Schmid J, Kowal DM, Bramlett DR, Miller TL, Tasse RP, Zaleska MM, Mayer JA (1998) *J Med Chem* **41**: 236
- [20] Kukhtin VA, Voskoboeva TN, Kirillova KM (1962) *Zh Obshch Khim* **32**: 2333; (1963) *Chem Abstr* **58**: 9127g
- [21] Tyryshkin NI, Fuzhenkova AV (1993) *Zh Obshch Khim* **63**: 792; *Chem Abstr* **119**: 226062j
- [22] Sharma D, Bansal RK (1990) *J Indian Chem Soc* **67**: 29
- [23] Sidky MM, Osman FH (1973) *Tetrahedron* **29**: 1725
- [24] Sidky MM, Osman FH (1971) *UAR J Chem* **14**: 225
- [25] Sidky MM, Osman FH (1973) *J Prakt Chem* **315**: 881
- [26] Well M, Fischer A, Jones PG, Schmutzler R (1992) *Phosphorus Sulfur* **71**: 143
- [27] Ramirez F, Desai NB (1960) *J Am Chem Soc* **82**: 2652
- [28] Ramirez F, Desai NB (1963) *J Am Chem Soc* **85**: 3252
- [29] Ramirez F, Bhatia SB, Patwardhan AV, Chen EH, Smith CP (1968) *J Org Chem* **33**: 20
- [30] Ramirez F, Ramanathan N (1961) *J Org Chem* **26**: 3041
- [31] Ogata Y, Yamashita M (1973) *J Org Chem* **38**: 3423
- [32] Mustafa A, Sidky MM, Soliman FM (1966) *Tetrahedron* **22**: 393
- [33] Sharma D, Bansal RK (1990) *J Indian Chem Soc* **67**: 29
- [34] Sidky MM, Soliman FM, El-Kateb AA (1976) *Indian J Chem* **14B**: 961
- [35] De Selms RC (1968) *Tetrahedron Lett* 5545
- [36] Ortiz de Montellano PR, Thorstenson PC (1972) *Tetrahedron Lett* 787
- [37] Schröder G (1963) *Die Entwicklung neuer insektizider Phosphorsäure-Ester*. Verlag Chemie GMBH, Weinheim/Bergstr, p 120
- [38] Mustafa A, Sidky MM, Soliman FM (1967) *Tetrahedron* **23**: 107
- [39] Sidky MM, Abdou WM, El-Kateb AA, Osman FH, Abd El-Rahman (1984) *Egypt J Chem* **27**: 817
- [40] Mahran MR, Khidre MD, Abdou WM (1995) *Phosphorus Sulfur* **101**: 17
- [41] Mahran MR, Abdou WM, Khidre MD (1990) *Monatsh Chem* **121**: 51
- [42] Sidky MM, Mahran MR, Boulos LS (1972) *J Indian Chem Soc* **49**: 383
- [43] El-Kateb AA, Abdel Malek HA (1995) *Egypt J Pharm Sci* **36**: 171
- [44] Magnus P, Halazy S (1985) *Tetrahedron Lett* **26**: 2985
- [45] Malysheva NA, Tumanskii BL, Khodak AA, Prokof'ev AI, Bubnov NN, Solodovnikov SP, Kabachnik MI (1987) *Iz Akad Nauk SSSR Ser Khim* 2563; (1989) *Chem Abstr* **110**: 23966y
- [46] Kutyrev AA, Moskva VV (1983) *Zh Obshch Khim* **53**: 2398; (1984) *Chem Abstr* **100**: 85809b
- [47] Osman FH, El-Samahy FA (2007) *Monatsh Chem* **138**: 545
- [48] Silverstien RM, Bassler GC, Morrill TC (1981) *Spectroscopic Identification of Organic Compounds*. John Wiley and Sons, New York
- [49] Milobendzki T, Sachnowski A (1917) *Chem Polski* **15**: 34; (1919) *Chem Abstr* **13**: 2865
- [50] Ford-Moore AH, Perr BJ (1951) *Organic Syntheses* **31**: 111
- [51] McCombei H, Saunders BC, Stacey GJ (1945) *J Chem Soc* 380
- [52] Gann PW, Heider RL (1954) US Patent 2,692,890; (1955) *Chem Abstr* **49**: 12529
- [53] Koelsch CF, LeClaire CD (1941) *J Org Chem* **6**: 516