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"α-METHYLENE-γ-PHOSTONES"[1] (5,5-DI- AND 5-MONOALKYL-2-METHOXY-3-METHYLENE-1,2-OXAPHOSPHOLAN-2-ONES). A PHOSPHORUS ANALOG OF THE ONE-STEP REFORMATSKY SYNTHESIS OF α-METHYLENE-γ-BUTYROLACTONES FROM KETONES AND ALDEHYDES

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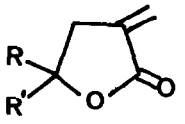
Abstract The first synthesis of "α-methylene-γ-phostones" (propylphostonates) using dimethyl bromo-3-propen-2 ylphosphonate and ketones and aldehydes, in the presence of zinc, is described

Because of their numerous biological activities[2], α-methylene-γ-butyrolactones have been the focus of a number of studies, especially of synthetic ones. Replacement of a carbon by a heteroatom has often resulted in the discovery of new compoundswith valuable properties Our interest in the mechanism of allergic contact dermatitis (ACD) to α-methylene-γ-butyrolactones[3] **1** prompted us to direct our attention to the synthesis of phosphorus analogs, cyclic phosphonates, α-methylene-γ-phostones **2**. Preliminary biological results (experimental induction of ACD in guinea-pigs and cytotoxicity in hepatoma tissue cultures) have shown that the biological activity of phostones is *very different* from that of the corresponding α-methylene-γ-butyrolactones (see below)



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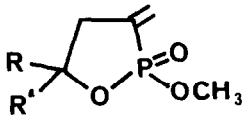

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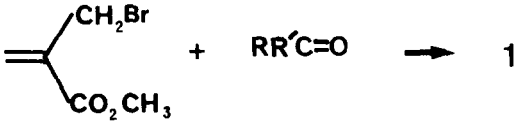
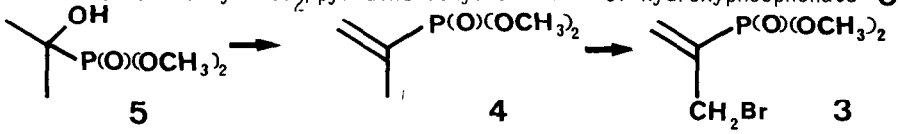
Among the numerous syntheses of α-methylene-γ-butyrolactones[4], an attractive one is the one-step Reformatsky reaction of methyl bromo-methacrylate with aldehydes and ketones[5]

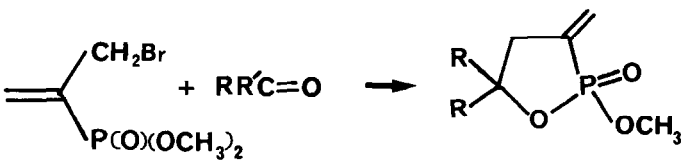


We thought we could use the same approach, by replacing the bromo-methacrylate derivative with a phosphonate such as **3**, containing an allylic bromide. The synthesis of this compound was readily accomplished by the NBS bromination[6] of ethylenic phosphonate **4**. The latter could be obtained by $SOCl_2$/pyridine dehydration[7] of hydroxyphosphonate **5**



5 **4** **3**

The Reformatsky-type reaction was accomplished by refluxing a THF solution of phosphonate **3** and a carbonyl derivative, in the presence of freshly powdered zinc The reaction was usually completed in less than an hour Table I summarizes the results with a number of carbonyl derivatives[8].



3 **2**

TABLE I. ONE STEP SYNTHESIS[a] OF α-METHYLENE-γ- PHOSTONES **2**

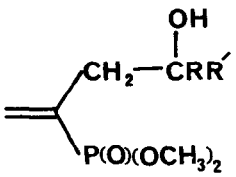
R	R'	Yield(%)[b]
H	H	63[c]
H	CH_3	65
H	C_2H_5	74
H	C_5H_{11}	70
CH_3	CH_3	87
C_2H_5	C_2H_5	69
$-(CH_2)_6-$		61
$-(CH_2)_7-$		50
$-(CH_2)_5-$		39
CH_3	C_6H_5	42

[a] *"α-Methylene-γ-phostones" were prepared by refluxing bromophosphonate* **3** *(0 500g, 2 18 mmol) with freshly ground Zn powder (0 150g, 2 29 mmol) and ketone or aldehyde (2 30 mmol) in THF (20 mL) for 1h, except for R = CH_3, R' = C_6H_5 and R,R' = $-(CH_2)_4$ which were reacted at room temperature for 24h ,* [b] *Calculated from the starting bromophosphonate* **3** , [c] *After two-steps formation of a hydroxyphosphonate* **6** *(63% yield) and p-TsOH cyclization (100% yield)*

The structures of phostones were deduced from elemental analysis, IR, NMR and mass spectrometry[8] In particular, for instance in the case of the dimethyl derivative(**2** ,R=R'=CH_3), the allylic protons appeared in NMR as a rough doublet of triplets(with a large *PCCH*-14Hz-coupling and a small, 2.0Hz, allylic coupling). The vinyl protons could easily be identified they appeared as a doublet of triplets centred at 5 83 and 5 93 ppm, the proton *cis* to phosphorus showing a small 21 7Hz coupling compared to a large 46.7Hz coupling for the *trans* proton[9] In spite of the presence of a chiral phosphorus center, neither the diastereotopic allylic protons nor the γ,γ-dimethyl groups show clear nonequivalence at 60MHz. The latter appeared as a broad singlet at δ1 45 ppm, the former appeared at first glance as a doublet of triplets However, the spectrum at 200MHz showed the allylic protons as a group of two nonidentical multiplets Use of $Eu(fod)_3$ shif reagent accentuated this difference, suggesting that the allylic protons had very close chemical shifts but different PCCH couplings The cyclic nature of compound **2** seems however well established from analytical and spectral data and also from the aspect of the nmr spectrum in the presence of a chiral shift reagent, $Eu(TFC)_3$[10] the $POCH_3$ signal appeared as two equally intense doublets, an evidence for the existence of a 1 1 racemic mixture

There was no evidence for the formation of a hydroxyphosphonate **6** (the "normal" Reformatsky product), except when the carbonyl compound used was formaldehyde[11]. This intermediate phosphonate was cyclized to the phostone by p-TsOH treatment. The mechanism of the Reformatsky reaction must be similar to that of an ordinary organometallic one, i e an ionic one However, there must be a radical component, since, when the reaction failed (when R or R' was aromatic except for R = CH_3, R' = C_6H_5),[12] the only compound which could be isolated was a substitution product of THF, compound **7** The anionic-radical nature of organometallic reactions, and in particular of Grignard ones, has been emphasized recently[13]

The formation of compound **7** could be ascribed to the formation of a radical, $CH_2 = C\left[P(O)(OCH_3)_2\right]CH_2^{\cdot}$ This single electron transfer mechanism[13] could also explain the formation of a byproduct found in all reactions, vinylphosphonate **4**[14]



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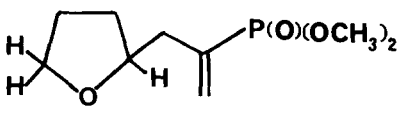

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The synthesis described here appears rather general one, except for most aromatic aldehydes and ketones. Whenever R ≠ R', the presence of diastereomers could be detected by NMR.

The first results concerning the sensitizing capacity of "α-methylene-γ-phostones" have shown that 1) they are *non sensitizers* in guinea-pigs[15], as opposed to the high sensitizing power of α-methylene-γ-butyrolactones[2,3] and 2) they are very little cytotoxic (they were almost without activity on hepatoma tissue culture cells except when R = C_5H_{11}).

ACKNOWLEDGEMENTS *We thank the DGRST for an "Allocation d'Etudes" (fellowship) to JNC (1980-1982), and Dr J P Beck for performing the cytotoxicity experiments*

REFERENCES AND NOTES

1 The name "phostonic acid" for cyclic phosphonic acid was used by Conant and Macdonald Conant, J B., Macdonald, A.D *J Amer Chem Soc.*, 1920, 42, 2337, and the word "phostonates" by Westheimer Eberhard, A., Westheimer, F H , *J Amer Chem Soc.*, 1965, 87, 253 The name "phostone" is the phosphorus equivalent of the lactones. The correct chemical Abstracts nomenclature is based on the 1,2-oxaphospholane nucleus.

2. See for instance Kupchan, S.M., Eakin, M.A., Thomas, A.M., *J Medicinal Chem* , 1971, 14, 1147 , Rodriguez E., Towers G.H N., Mitchell J C., *Phytochemistry*, 1976, 15, 1573.

3. Corbet J P , Benezra C , *J Org Chem* , 1981, 46, 1141 , Schlewer G , Stampf J L., Benezra C., *J Medicinal Chem* , 1980, 23, 1031 , Dupuis G., Benezra C , Schlewer G , Stampf J.L., *Molecular Immunology*, 1980, 17, 1045

4 Grieco P A., *Synthesis*, 1975, 67

5. Loffler A., Pratt R D., Pucknat J , Gelbard G , Dreiding A S , *Chimia*, 1969, 23, 413 , Reininger K , Schmidt U., *Angew Chem Intern Edit.*, 1970, 9, 457

6. Djerassi C., *Chem Rev* , 1948, 43, 271.

7 Benezra C., Nešić S., Ourisson G , *Bull. Soc Chim France*, 1967, 1140

8 Dimethyl-3-bromo-2-methylene-2-ethylphosphonate **3** was prepared as follows dimethyl 2-methylene-2- ethylphosphonate **4** (0 500g, 3 33 mmol) and N-bromosuccinimide (NBS, 0.593 g, 3.33 mmol) were mixed in 10 mL CCl_4, AIBN (0.005g) was added and the mixture was refluxed for 3h. After this time, no more NBS was present and succinimide floated at the surface of the CCl_4 Filtration and removal of the solvent under vacuum gave a mixture which was deposited on a 50g SiO_2 column Elution with ethyl acetate gave the bromo derivative (0 532 mg, 2.32 mmol, 70% yield) and then the unreacted starting material **4** (0 120g, 0.800 mmol). Compound **3** oil , ^{1}H NMR ($CDCl_3$) 3.76 (d, 6H, $POC\underline{H}_3$, J = 11,3 Hz), 4 12 (dt, 2H, $PCC\underline{H}_2Br$, J = 13.0 and 1.2 Hz) 6 23 (dt, 1H, C = $C\underline{H}_{trans}$, J = 44.0 and 1 2 Hz). 6.25 (dt, 1H, C = CH_{cis} J = 20 3 and 1 0 Hz), IR ($CHCl_3$) 1270, 1190, 1040-1060 cm^{-1} , MS 230, 228 ($M^{+\cdot}$), 150, 149, 135, 110, 109 , Anal. Calc for $C_5H_{10}BrO_3P$ C 26,21, H 4.37, P. 13.54, Fd C 26.58 H 4 00, P 13.40

The "α-methylene-γ- phostone" **2** (R=R'=CH_3) was prepared by refluxing bromophosphonate **3** (0.500g, 2 18 mmol) with freshly ground Zn powder (0.150g, 2.29 mmol) and acetone (0.133g, 2.30 mmol) in THF (20 mL) for 1h. After this reaction time, the mixture was hydrolyzed with HCl 1N (20 mL) and extracted with CH_2Cl_2 (50 mL x 3), dried with magnesium sulfate and solvent removed The mixture was separated in a silica gel column (100 times the weight of crude) and elution with ether gave "phostone" **2** , (0.335g, 1 90 mmol, 87% yield) and then dimethyl 2-methylene-2-ethylphosphonate **4** (0.030g, 0.200 mmol) Compound **2** (R=R'=CH_3) oil , ^{1}H NMR ($CDCl_3$, Me_4Si) 1.45 (s, 6H, $C\underline{H}_3$), 2.73 (dt, 2H, $PCC\underline{H}_2$, J = 14 and 2 0 Hz), 3.73 (d, 3H, $POC\underline{H}_3$, J = 11 3 Hz), 5.83 (d of t, C = CH_{trans}, J = 46.7 and 2.0 Hz), 5 93 (dt, C=CH_{cis}, J = 21.7 and 2.3 Hz) , IR ($CHCl_3$) 1260, 1190, 1030 cm^{-1}, mass spectrum m/e 176 (M^+), 161, 149, 79. Anal Calcd for $C_7H_{13}O_3P$ C 47.73 , H, 7.38 , P, 17,61. Found C, 47.94 , H, 7 58 , P, 17 52.

9. Benezra C , *J Amer. Chem. Soc.*, 1973, 95, 6890.

10 Tris [3-(2,2,2-trifluor-1-hydroxyathyliden)-d-camphorato] europium, "uvasol ®", from Merck the mole ratio was 7 5 100 shift reagent/phostone.

11. Hydroxyphosphonates were also formed when the reaction was conducted with aldehydes at *room temperature* This was shown by NMR two $POCH_3$ were present (as compared to *one* $POCH_3$ in the phostone).

12. Compound **7** oil, ^{1}H NMR ($CDCl_3$, Me_4Si) 1.2-2.2 (m, 4H), 2.47 (d of d, 2H, $PCC\underline{H}_2$, J = 14 3 and 6.3 Hz), 3 70 (d, 6H, $POC\underline{H}_3$, J = 10.8 Hz), 3 6-4.3 (m, 3H), 5.98 (d of d of d, C = CH_{trans}, J = 48 3 and 1.4 Hz), 6 12 (d of d of d, C = CH_{cis}, J = 23.3 and 0.8) , IR ($CHCl_3$) 1240, 1180, 1050-1030 cm^{-1} , mass spectrum m/e 221 (M^+ + 1), 150, 110, 96, 71.

13. Ashby E.C., Bowers Jr, J R., *J Amer Chem. Soc.*, 1981, 103, 2242.

14. The formation of this compound could also be explained by the hydrolysis of the unreacted organozinc derivative.

15. For R=R'=CH_3, guinea-pigs were intradermally injected with a dispersion of compound **2** (5%) in a 1 1 Saline/Freund Complete Adjuvant mixture See reference 3 (Schlewer and al) for detailed procedure of sensitizations

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