α-Keto Phosphonoacetates

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Oxophosphonoacetate (**1**), a novel biophosphate analogue containing a highly reactive α-ketone function at pH <7, proved inaccessible by direct hydrolysis of its previously unsynthesised triethyl ester (**2**), but can be made by oxygen transfer to the α-carbene of ethyl *P,P*-bis(trimethylsilyl) phosphonoacetate followed by heating in H_2O.

Phosphonoacetic acid (PAA) strongly inhibits several herpes virus nucleic acid polymerases,[1,2] but is ineffective as an inhibitor of reverse transcriptase (RT) from human immunodeficiency virus type 1 (HIV-1), believed to be the cause of AIDS. In contrast, phosphonoformic acid (PFA), the norhomologue of PAA, is a potent inhibitor of RT.[3] It is not known how the interposed CH_2 group in PAA *vs.* PFA produces this striking difference, but recently it was shown that carbonyldiphosphonate is a moderately good inhibitor of RT, whereas the corresponding methylene compound is inactive.[3] These observations suggest that evaluation of oxophosphonoacetate (**1**) (phosphonoglyoxylate) as a polymerase inhibitor might provide useful information. More generally, the presence in (**1**) of an unusually reactive α-keto group would offer the possibility of covalent bond formation at a site where the molecule is reversibly bound. This potential labelling might be precluded were the ketone to prove so reactive that it hydrated completely at physiological pH.

Prior claims for synthesis of the triethyl ester (**2**) of oxophosphonoacetic acid *via* Michaelis–Arbuzov reaction between ethyl oxalyl chloride and triethyl phosphite have been made,[4,5] but we find them to be unsubstantiable.‡ Alkaline hydrolysis of gem-dichlorophosphonoacetate,[2,6] by analogy to Quimby's preparation of carbonyldiphosphonate,[7] leads to scission of the C–P bond; methods successfully used to oxidize diethyl malonate to diethyl oxomalonate[8] fail when applied to triethyl phosphonoacetate (**3**). However, we find that the pronounced electron deficiency of the methylene carbon in (**3**), which makes it resistant to direct oxidation, can be exploited using carbene-mediated oxygen transfer chemistry.[9] Thus, thermal decomposition of triethyl diazophosphonoacetate[10] (**4**), catalysed by rhodium(II) acetate, with propylene oxide gave (**2**) as a distillable, brilliant greenish-yellow oil [b.p. 84—86 °C (0.001 mmHg)] characterised by ^1H n.m.r., ^{13}C n.m.r. [δ 193.5 (d, *J* 196 Hz); δ 159.6 (d, *J* 76 Hz); ethyl resonances], ^{31}P n.m.r. (δ −2.4 p.p.m.), i.r., u.v., and elemental analysis (n.m.r. samples in $DCCl_3$).

Although stable under anhydrous conditions, (**2**) hydrates quantitatively in H_2O, giving the gem-diol (**7a**) [^{13}C n.m.r. δ 169.4 (d, *J* 16 Hz); δ 93.2 (d, *J* 200 Hz); ethyl resonances; ^{31}P n.m.r. δ 13.5 p.p.m., both samples in neutral D_2O]. Addition of a partial equivalent of water led to a ketone/hydrate mixture whose components do not exchange on the n.m.r. time scale. Methanol also adds quantitatively to form hemiketal (**7b**); this adduct does not liberate methanol when held in water for 1 day at 25 °C. However, when (**2**) is treated with the more hindered t-amyl alcohol, only about 5% reacts to form hemiacetal (**7c**).

De-esterification of (**2**) by conventional hydrolysis using aqueous HCl, HBr, or sodium hydroxide led to decomposition; treatment of the ester with chloro-, bromo-, or iodotrimethylsilane gave complex reaction mixtures presumably arising from reactions between the silylating agent and the reactive α-keto group. This impasse was resolved by preliminary silyldealkylation[11] of (**4**) to give ethyl *P,P*-bis(trimethylsilyl)diazophosphonoacetate, followed by oxygen transfer to the carbene generated as described above to give the corresponding mixed ester of oxophosphonoacetate, (**5**). Treatment of (**5**) with water selectively[12] removed the trimethylsilyl groups, giving an aqueous solution of the monoethyl ester (**6**); this was heated to 56 °C for 26 h to complete the ester hydrolysis. The α-keto phosphonic monoacid (**1b**) was recovered as a bis(dicyclohexylammonium) salt (**8**) [m.p. 159—160 °C (dec.)] ^{31}P n.m.r. (H_2O, pH 5.5): δ −1.2 p.p.m. (**1**) and 14.5 p.p.m. (**9**) in an integrated peak ratio of 4:6; satisfactory elemental analysis obtained. The structure has also been confirmed by *X*-ray crystallographic analysis.

An interesting feature of (**1**) is the marked, pH-dependence of its ketone–hydrate equilibrium. Investigation by u.v. and ^{31}P n.m.r. spectroscopy disclosed more than 99.9% of the trianion to be present as the ketone (**1a**) in the alkaline pH region. As the pH is decreased below 7, formation of a

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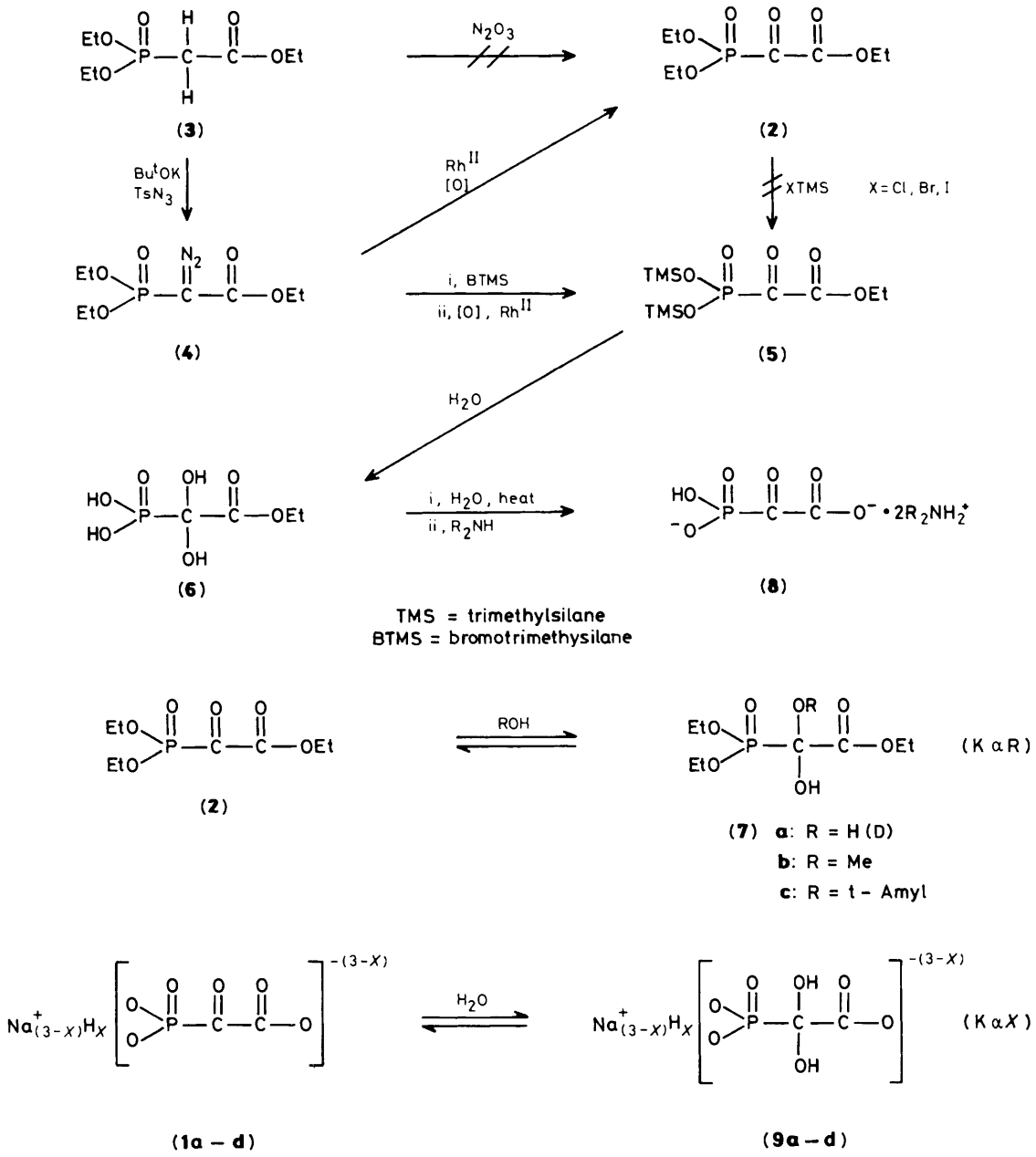
‡ In both cases, reported characterisation of the reaction product was limited to a refractive index (in ref. 4 it is claimed to be an undistillable liquid). In our hands, ^{31}P n.m.r. analysis of mixtures obtained from the reactants cited revealed multiple phosphorus-containing products, none of which were spectroscopically identifiable as (**2**).



significant amount of dianion (**1b**) [and, eventually, monoanion (**1c**)] leads to formation of observable amounts of hydrated species, which predominate below pH 6. This can be ascribed to the effect of decreased negative charge in anions (**1b**) and (**1c**), which increases the electrophilicity of the α-keto carbon atom, leading to a larger fraction of hydrate (**9**). At physiological pH, the acid–base equilibria of (**1**) and (**9**) are such that the unhydrated ketone forms are predominant in H_2O, but these are likely to add a stronger nucleophile; transfer of these species from bulk solvent into a cationic environment that would significantly lessen their negative charge is predicted to augment their α-carbonyl group reactivity, potentially leading to site-activated addition of proximate nucleophiles. Investigation of the interaction of (**1**) with viral polymerases is in progress.

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