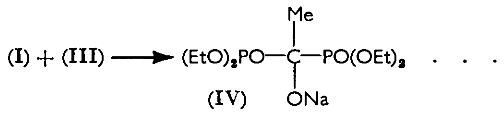
449. *Methylenebisphosphonates and Related Compounds. Part II.*[1] *Synthesis from α-Keto-phosphonates.*

By J. A. CADE.

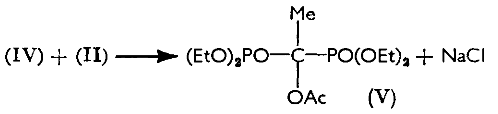
By the interaction of dialkyl hydrogen phosphites and dialkyl α-keto-phosphonates in the presence of a base, tetra-alkyl 1-hydroxyalkane-1 : 1-bisphosphonates $(RO)_2PO{\cdot}CR'(OH){\cdot}PO(OR'')_2$ are formed. Some symmetrical and unsymmetrical alcohols are described.

IN an unsuccessful attempt to prepare diethyl acetylphosphonate (III) by interaction of sodium diethyl phosphite and acetyl chloride, Arbusov and Azanovskaya[2] obtained as the main product of the reaction, tetraethyl 1-ethoxycarbonylethylidenebisphosphonate (V). They showed that the reactions involved were (1)—(3), for by starting with keto-phosphonate (III), sodium dialkyl phosphite, and acetyl chloride, the sequence (2)—(3) could be realised independently:

$$\underset{\text{(I)}}{(EtO)_2PO{\cdot}Na} + \underset{\text{(II)}}{AcCl} \longrightarrow \underset{\text{(III)}}{(EtO)_2P(O){\cdot}CO{\cdot}CH_3} + NaCl \quad . \; . \; . \; . \; . \; . \; . \; . \quad (1)$$



$$\text{(I)} + \text{(III)} \longrightarrow \underset{\text{(IV)}}{(EtO)_2PO}\!-\!\underset{ONa}{\overset{Me}{C}}\!-\!PO(OEt)_2 \quad . \; . \; . \; . \; . \; . \; . \; . \; . \quad (2)$$



$$\text{(IV)} + \text{(II)} \longrightarrow (EtO)_2PO\!-\!\underset{OAc}{\overset{Me}{C}}\!-\!PO(OEt)_2 + NaCl \quad \text{(V)} \quad . \; . \; . \; . \; . \; . \; . \quad (3)$$

The intermediate alcohol corresponding to (IV) was not isolated, but recently examples of such compounds prepared by this method but with an organic base in place of sodium have been reported.[3] Some new 1 : 1-bisphosphono-alcohols, $(RO)_2PO{\cdot}CR'(OH){\cdot}PO(OR)_2$, are

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[1] Part I, preceding paper.

[2] Arbusov and Azanovskaya, *Doklady Akad. Nauk S.S.S.R.*, 1947, **58**, 1961.

[3] McConnell and Coover, *J. Amer. Chem. Soc.*, 1956, **78**, 4450.

now described, and it has been shown that the reaction can be effected with much less than one equivalent of sodium.[4] A trace of organic tertiary base could also be employed to initiate the reaction but offered no advantage over sodium because acidic by-products tended to hold the base back until the desired product was distilling, whereupon it was liberated and contaminated the latter.

The new alcohols and their physical constants are listed in Table 1; Table 2 contains analytical data. Most of the are colourless, practically odourless liquids. Lorentz–Lorenz molar refractivities $[R_L]_D$, were deduced from the observed physical constants and provide evidence of composition. Calculated values were computed from the atomic values for oxygen and phosphorus derived by Kabachnik [5] and group values of the organic residues given by Vogel.[6] The infrared spectra of the compounds will be described in a subsequent paper.

The stated crude yields were reproducible for reactions carried out on an approximately 0·25 molar scale. On a larger scale, the yields, in particular of the unsaturated esters, were lower, and larger residues were obtained, probably as a result of the prolonged heating necessary to distil proportionately larger quantities. Those compounds in which R, R′, or R″ were unsaturated were of particular interest since resins containing the essential

TABLE 1.

		Compound						
No.	R	R′	R″	Yield (%) *	B. p./mm.	n_D^t	d_4^t	$t°$
1 †	Me	Me	Me	30	126—128°/0·07	1·4300	1·269	25
2 †	Et	Me	Et	67	125°/0·06	1·4350	1·154	20
3	A	Me	A	55	137°/0·15	1·4615	1·137	20
4 †	Pr^i	Me	Pr^i	63	115°/0·06	1·4326	1·072	20
5	Bu	Me	Bu	72	159°/0·12	1·4364	1·039	25
6 †	Me	Me	Et	35	124—128°/0·07	1·433	—	20
7	Et	Me	A	42	126—128°/0·01	1·455	—	20
8 †	Et	Me	Pr^i	40	124—129°/0·1	1·434	—	20
9	Et	Me	Bu	35	130°/0·05	1·4370	1·087	25
10	Me	Ph	Me	—	‡	—	—	—
11	Et	Ph	Et	72	149°/0·07	1·4798	1·180	25
12	Bu	Ph	Bu	50	180—184°/0·1	1·4786	1·064	20
13 †	Me	X	Me	36	140—142°/0·1	1·436	—	25
14 †	Et	Y	Et	—	‡	—	—	—

A = allyl, $CH_2{:}CH{\cdot}CH_2$–; X = propenyl, CHMe:CH–; Y = CHMe:CH·CH:CH–.

* Crude. Purification before characterisation was at expense of yield. † H_2O-miscible. ‡ Does not distil.

TABLE 2.

Compound	Formula	Found (%) C	H	P	$[R_L]_D$	Required (%) C	H	P	$[R_L]_D$
1	$C_6H_{16}O_7P_2$	27·5	6·1	23·4	53·36	27·5	6·15	23·6	52·92
2	$C_{10}H_{24}O_7P_2$	38·55	7·7	20·3	72·0	37·75	7·6	19·5	71·52
3	$C_{14}H_{24}O_7P_2$	45·7	6·7	16·7	88·48	45·9	6·6	16·9	88·40
4	$C_{14}H_{32}O_7P_2$	44·4	8·6	16·7	90·64	44·9	8·6	16·55	90·24
5	$C_{18}H_{40}O_7P_2$	50·0	9·3	14·3	108·43	50·2	9·4	14·4	108·68
6	$C_8H_{20}O_7P_2$	—	—	20·9	*	—	—	21·35	—
7	$C_{12}H_{24}O_7P_2$	—	—	18·0	*	—	—	18·1	—
8	$C_{12}H_{28}O_7P_2$	—	—	17·3	*	—	—	17·9	—
9	$C_{14}H_{32}O_7P_2$	44·6	8·5	16·3	90·22	44·9	8·6	16·55	90·10
10	$C_{11}H_{18}O_7P_2$	—	—	18·9	*	—	—	19·1	—
11	$C_{15}H_{26}O_7P_2$	47·3	6·9	16·3	91·54	47·4	6·9	16·3	91·23
12	$C_{23}H_{42}O_7P_2$	58·7	8·7	11·75	131·15	56·1	8·6	12·6	128·39
13	$C_8H_{18}O_7P_2$	32·5	6·8	20·9	*	33·3	6·3	21·5	—
14	$C_{14}H_{28}O_7P_2$	46·2	7·6	15·35	*	45·4	7·6	16·7	—

* Insufficiently pure ester available.

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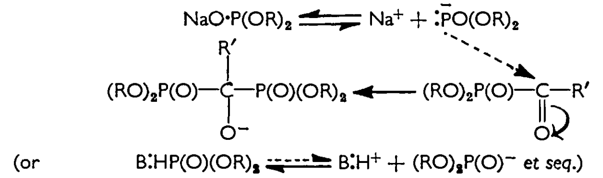
[4] Cade, A.E.R.E. Report, C/R 2012, 1957.

[5] Kabachnik, *Bull. Acad. Sci. U.S.S.R.*, 1948, 219.

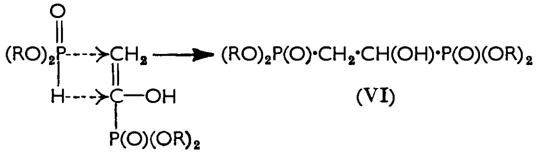
[6] Vogel, " Textbook of Practical Organic Chemistry," Longmans, London, 1948, p. 898.

–P(O)·C·P(O)– bridge could be derived from them,[1] but an opportunity was taken of investigating the general applicability of the method.

Evidence concerning the mechanism of this type of reaction is not yet available but, from the qualitative observations that the reaction is base-catalysed and that the higher alkyl phosphites react more sluggishly, it may be provisionally depicted as a pre-ionisation followed by nucleophilic attack,[3] the latter being rate-determining:



The possibility that for acetylphosphonates the process may be a Michael-type addition resulting in formation of an ethylenebisphosphonate (VI), was not overlooked,[7] although keto-enol tautomerism in α-keto-phosphonates has not yet been established:



The reaction between diethyl acetylphosphonate and dibutyl hydrogen phosphite was complicated by transesterification, as was that between diethyl hydrogen phosphite and dibutyl acetylphosphonate. Each reaction, however, gave among its products the same dibutyl diethyl 1-hydroxyethylidenebisphosphonate. The identity of the products was based on the concurrence of physical properties and analysis, and the virtually identical infrared spectra.

This observation is good evidence that addition occurs across the double bond of the carbonyl group. Further, benzoylphosphonates, which cannot exhibit keto–enol tautomerism, readily undergo the reaction.

EXPERIMENTAL

α-Keto-phosphonates.—The esters were prepared in the usual manner [8] by adding trialkyl phosphite (1 mol.) to acid chloride (1·1 mol.) at −10°, allowing the mixture to attain room temperature, and distilling the products. New keto-phosphonates were: *Diallyl* (50—67% yield), b. p. 71°/0·25 mm., n_D^{20} 1·4534, d_4^{20} 1·105 (Found: C, 47·0; H, 6·4; P, 15·1%; $[R_L]_D$ 50·00. $C_8H_{13}O_4P$ requires C, 47·1; H, 6·4; P, 15·2%; $[R_L]_D$ 49·17), and *di-isopropyl acetylphosphonate* (62—72%), b. p. 56°/0·1 mm., n_D^{20} 1·419 (Found: P, 14·8. $C_8H_{17}O_4P$ requires P, 14·9%); *dibutyl benzoylphosphonate* (65%), b. p. 160—164°/0·1 mm., n_D^{20} 1·4975 (Found: P, 10·4. $C_{15}H_{23}O_4P$ requires P, 10·4%); *dimethyl crotonoylphosphonate* (30%), b. p. 65—68°/0·05 mm., n_D^{25} 1·463 (Found: P, 17·3. $C_6H_{11}O_4P$ requires P, 17·4%); *diethyl hexa-2 : 4-dienoylphosphonate* (49%), b. p. 106—110°/0·07 mm., n_D^{25} 1·503 (Found: P, 13·0. $C_{10}H_{17}O_4P$ requires P, 13·3%).

Dialkyl Hydrogen Phosphites.—Redistilled commercial products were used, but diallyl hydrogen phosphite was prepared as described in Part I.[1]

Tetra-alkyl 1-Hydroxyalkylidenebisphosphonates.—To a mixture of dialkyl acetylphosphonate (0·25 mole) and excess of dialkyl phosphite (0·3 mole) was added sodium (0·01 g.-atom) dissolved in the minimum quantity of alcohol having the same alkyl group as that of the hydrogen phosphite. This reduced the chance of transesterification in preparation of unsymmetrical esters in which R ≠ R′. The temperature of the mixture rose spontaneously by 20—60° and was

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[7] Kennedy, personal communication.

[8] Kosolapoff, "Organophosphorus Compounds," Wiley, New York, 1950, p. 122.

kept about 50° higher than the maximum initially attained for 2—4 hr. The exothermicity was governed by the nature of the alkyl groups; thus the di-isopropyl esters reacted more sluggishly than the ethyl esters in equivalent conditions. After reaction volatile matter was removed and the residue was separated into two main fractions by distillation at low pressure. Redistillation of the higher-boiling fraction afforded the pure tetra-ester in 50—70% yields.

An alternative procedure useful for obtaining higher analogues (especially where R′ = Ph) was to add the keto-phosphonate to a pre-prepared solution in benzene of an equivalent of the sodium dialkyl phosphite, heat the whole under reflux for 2—4 hr., and separate the product after aqueous treatment which removed acidic impurities as the sodium salts.

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