in the synthetic process were remained in peptide IV. From the results of this study (Fig. 3), however, no peptides employed modified the pressor effect of vasopressin even in considerably large doses up to 16 mg/kg *i.v.*, although they reduced blood pressure and heart rate in rats. Consequently, it seems reasonable to conclude that they would possess no antagonistic activity against vasopressin on rat blood pressure. These results are in contrast to those of the antagonistic action to oxytocin in the isolated rat uterus.[3,4] This discrepancy may be due to the organ difference or difference of the active sites of vasopressin from those of oxytocin.

Most of the peptides produced, more or less, vasodilation in dog hindquarter and coronary vascular beds, although the coronary perfusion was undertaken only in one animal due to the deficiency of the peptides available. It is indicated that in both the blood pressure lowering and vasodilatory effects, the potencies of the peptides examined did not correlate with the length of amino acid sequence.

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# Reaction of Alkyl Dialkoxyphosphinyl Formate with Strong Base

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In 1966, Shahak[2] reported that ketones were carbalkoxylated in the α-position with ethyl diethoxyphosphinyl formate (EDEPF) in the presence of sodium hydride, *via* an intermediate $[R\cdot CO\cdot CR'\cdot CO\cdot P(=O)(OEt)_2]^-Na^+$, in good yield.

We attempted to apply this method to the preparation of ethyl 2-oxo-5-phenylcyclohexanecarboxylate from 4-phenylcyclohexanone (I). However, the sole product isolated from the reaction mixture was 1-diethoxyphosphinyl-4-phenylcyclohexanol (III), mp 110—111°. Therefore, we reexamined the reaction of cyclohexanone (II) with EDEPF according to the Shahak's procedure, and could not obtain the β-ketoester but 1-diethoxyphosphinylcyclohexanol (IV).[3]

On the other hand, it had been reported that EDEPF was decomposed by refluxing with aqueous sodium hydroxide solution into carbon dioxide and phosphorous acid, accompanying formation of phosphonoformic acid in low yield.[4] This fact implies that in a protic solvent hydroxide ion attacks at both the carbonyl carbon and the phosphorus atom of EDEPF. Thus, we examined the behavior of EDEPF, methyl diethoxyphosphinyl formate (MDEPF), ethyl diemthoxyphosphinyl formate (EDMPF) and methyl dimethoxyphosphinyl formate (MDMPF) with several strong bases, such as hydride, amide, ethoxide and methoxide anion, in benzene, in order to search any clue to resolve the above discord and to find the optimum condition for the carbalkoxylation of ketones with alkyl dialkoxyphosphinyl formate. The results are illustrated in Table I.

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1) Location: *Hongo, Toyama.*
2) I. Shahak, *Tetrahedron Letters*, **1966**, 2201.
3) V.S. Abramov, *Zhur. Obshchei Khim.*, **22**, 647 (1952) [*C. A.*, **47**, 5351 (1953)].
4) *a*) P. Nylen, *Ber.*, **57**, 1023 (1924); *b*) S. Warren and M.R. Williams, *J. Chem. Soc.* (*B*), **1971**, 618.

Table I. Reaction of Alkyl Dialkoxyphosphinyl Formate with Strong Bases in Benzene

| Compound | Base | Reaction time, Min. (Temp. °C) | Products isolated[a], % yield[b] | | |
|---|---|---|---|---|---|
| | | | $(MeO)_2CO$ | MeOCOOEt | $(EtO)_2CO$ |
| $(EtO)_2P(=O)CO_2Et$ | NaH | 60(15)+60(80) | — | — | 36 |
| | $NaNH_2$ | 60(15)+60(80) | — | — | 39 |
| | NaOEt | 45(15)+10(80) | — | — | 82 |
| | NaOMe | 45(15)+10(80) | 8 | 29 | 40 |
| | NaOMe | 6( 0) | 7.5 | 36 | 41 |
| $(EtO)_2P(=O)CO_2Me$ | NaH | 60(15)+60(80) | 10 | 12 | 4 |
| | NaH | 180(15) | 12 | 8 | 2 |
| | $NaNH_2$ | 60(15)+60(80) | trace | 10 | 22 |
| | NaOEt | 45(15)+10(80) | 3.5 | 20 | 53 |
| | NaOMe | 45(15)+10(80) | 20 | 42 | 25 |
| | NaOMe | 6( 0) | 28 | 48 | 18 |
| $(MeO)_2P(=O)CO_2Et$ | NaH | 60(15)+60(80) | 3.5 | 14 | 5 |
| | $NaNH_2$ | 60(15)+60(80) | 8 | 16 | 8.5 |
| | NaOEt | 45(15)+10(80) | 16 | 44 | 30 |
| | NaOEt | 6( 0) | 8.5 | 40 | 30 |
| | NaOMe | 45(15)+10(80) | 36 | 36 | 8 |
| $(MeO)_2P(=O)CO_2Me$ | NaH | 60(15)+60(80) | 19 | — | — |
| | $NaNH_2$ | 60(15)+60(80) | 20 | — | — |
| | NaOEt | 45(15)+10(80) | 30 | 40 | 17 |
| | NaOMe | 45(15)+10(80) | 61 | — | — |
| | NaOMe | 6( 0) | 73 | — | — |

*a*) The products were isolated by preparative gas chromatography and characterized by comparison of the IR spectra and the retention times in gas chromatography with those of authentic samples.
*b*) Analysis by gas chromatography on a 1 m×3 mm PEG-6000 (25% on Shimalite) at 60°.

As seen in Table I, it is clear that the carbon-phosphorus bond of alkyl dialkoxyphosphinyl formate ($RO\cdot CO\cdot P(=O)(OR')_2$) is easily cleaved by a strong base, and that a base attacks at both the phosphorus atom and the carbonyl carbon atom. When the phosphorus atom is attacked, a nucleophilic substitution takes place to give $R'O^-$ and $RO\cdot CO\cdot P(=O)B(OR')$ (A) (type a reaction); while, when the carbon atom is attacked, one of the two bonds of carbon-oxygen (type b reaction) and carbon-phosphorus (type c reaction) is cleaved to give either $RO^-$ and $B\cdot CO\cdot P(=O)(OR')_2$ (B) or $^-P(=O)(OR')_2$ and $RO\cdot CO\cdot B$ (C). The alkoxide anions formed in type a and b reactions also play the role of base. The primary products A and B would also undergo the similar reactions. Moreover, the alkoxyl group of the carbonates would be exchanged with a base, and alkyl formate formed in the reaction of alkyl dialkoxyphosphinyl formate with sodium hydride may be decomposed into hydrogen, carbon monoxide and sodium alkoxide.[5] The complex reaction sequence may be represented by the following equations.

$$RO\cdot CO\cdot P(=O)(OR')_2 \xrightarrow[\text{attack at P}]{B^-} RO\cdot CO\cdot \overset{O^-}{\underset{B}{P}}(OR')_2 \xrightarrow{\text{type a}} RO\cdot CO\cdot \overset{O}{\underset{B}{P}}(OR')\ (A) + {}^-OR'$$

$$RO\cdot CO\cdot P(=O)(OR')_2 \xrightarrow[\text{attack at C}]{B^-} RO\cdot \overset{O^-}{\underset{B}{C}}\cdot P(=O)(OR')_2 \xrightarrow{\text{type b}} {}^-OR + B\cdot CO\cdot P(=O)(OR')_2\ (B)$$

$$RO\cdot CO\cdot P(=O)(OR')_2 \xrightarrow[\text{type c}]{} [P(=O)(OR')_2]^- + RO\cdot CO\cdot B\ (C)$$

5) J.C. Powers, R. Seidner, and T.G. Parsons, *Tetrahedron Letters*, **1965**, 1713.

Thus, it may be concluded that in the reaction of alkyl dialkoxyphosphinyl formate with a strong base the simple exchange of the alkoxyl group of the ester (type b reaction) is, at least, not the main reaction; accordingly, formation of III and IV in the reaction of I and II with EDEPF would be caused by decomposition of EDEPF into ethyl formate and sodium diethyl phosphite, which in turn reacts with I and II.

From these results and consideration, it was assumed that for the carbalkoxylation of an ordinary ketone with alkyl dialkoxyphosphinyl formate, the ketone must be completely converted to the enolate ion prior to addition of the phosphinyl formate. Thus, carbalkoxylation of II was carried out as follows: a mixture of II and sodium hydride in benzene was refluxed for 15 hours, and then EDEPF was added. From the reaction mixture ethyl 2-oxocyclohexanecarboxylate (V)[6] was obtained in about 40% yield. The similar reaction of II with MDEPF afforded methyl 2-oxocyclohexanecarboxylate (VI)[7] in about 50% yield. These facts suggest that the carbalkoxylation of ordinary ketones with alkyl dialkoxyphosphinyl formate involves mainly the direct carbalkoxylation accompanying elimination of diethyl phosphite.

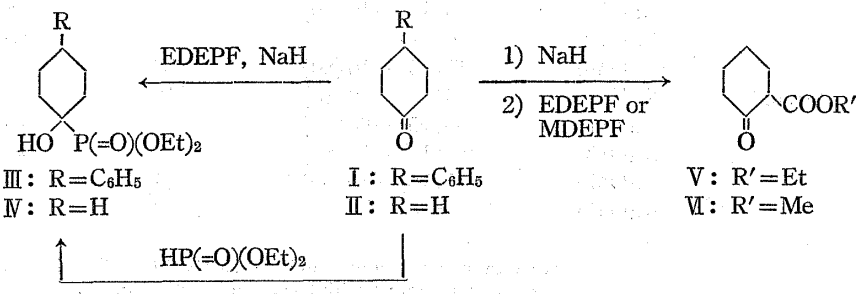


Chart 1

## Experimental[8]

**Reactions of EDEPF with 4-Phenylcyclohexanone (I) and Cyclohexanone (II)**——i) To a suspension of 3 g of 50% suspension of NaH in mineral oil in 150 ml of dry dioxane was added 13 g of freshly distilled EDEPF[4] in one portion, followed by addition of 11 g of I in 30 ml of dry dioxane at room temperature during 10 min, then 2 drops of EtOH were added. After stirring for 1 hr at the temperature, *ca.* 10 ml of the solvent was distilled at 60° under aspirator pressure. The reaction mixture was allowed to stand for 1 hr at room temperature, then poured into 200 ml of absolute EtOH containing 13 g of conc. $H_2SO_4$. After stirring for 1 hr, the mixture was poured into 600 ml of water and extracted with ether several times. The combined extracts were washed with saturated NaCl solution and dried over $Na_2SO_4$. The residue of the extract was distilled *in vacuo* to give 6 g of colorless distillate of bp 100—120° (3 mmHg), which was proved to be I by comparison of the IR spectra. The solid residue of the distillation was recrystallized from ether to give 5.5 g of III, mp 110—111° (colorless cubes). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3270 (OH), 1225 (P=O), 1065, 1035 (P–OC). NMR ($CDCl_3$) $\tau$: 2.78 (one peak, 5H, arom. H), 5.79 (double quartet, $J_{HH}$=8.0 Hz, $J_{PH}$=7.5 Hz, 4H, P–O–$CH_2CH_3$), 6.40 (singlet, 1H, –OH, disappeared by treatment with $D_2O$), 7.25—8.50 (complex multiplet, 9H, aliph. H), 8.65 (double triplet, $J_{HH}$=8.0 Hz, $J_{PH}$=1.0 Hz, 6H, P–O–$CH_2CH_3$). Mass Spectrum Calcd. for $C_{16}H_{25}O_4P$: MW, 312.149. Found: $M^+$, 312.143. *Anal.* Calcd. for $C_{16}H_{25}O_4P$: C, 61.52; H, 8.07. Found: C, 61.24; H, 7.99. An authentic sample of III was prepared as follows: to a mixture of 2 g of I and 1.5 g of diethyl phosphite was added 2 drops of 10% NaOMe in MeOH, and the mixture was allowed to stand for few minutes. The resultant solid mass was recrystallized from ether to give 2 g of colorless cubes, mp 110—112°. The IR spectrum of this sample was superimposable with that of the sample obtained in the above.

ii) To a suspension of 0.5 g of NaH (50% suspension in mineral oil) in 15 ml of di-*n*-butyl ether was added 2.1 g of freshly distilled EDEPF in one portion, followed by addition of 1 g of freshly distilled II in three portions at room temperature under stirring, then 1 drop of EtOH was added. After stirring for 1 hr

6) H.R. Snyder, L.A. Brooks, and S.H. Shapiro, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, N.Y., 1943, p. 531.
7) R. Levine and C.R. Hauser, *J. Am. Chem. Soc.*, **66**, 1768 (1944).
8) Melting points were taken with a Yanagimoto Micro Melting Point Apparatus and uncorrected. NMR spectra were taken on a JNM-C-60H spectrometer using TMS as an internal standard.

at the temperature, *ca.* 2 ml of the solvent was distilled off at 60° under aspirator pressure. The reaction mixture was cooled to the room temperature and allowed to stand for 1 hr, then poured into 15 ml of absolute EtOH containing 1.5 g of conc. $H_2SO_4$. After stirring for 1 hr, the mixture was poured into 100 ml of water and the resulting layers were separated. The aqueous layer was extracted three times with benzene. The combined organic layers were washed with saturated NaCl solution and dried over $Na_2SO_4$. The residue of the organic solution which solidified on standing was recrystallized from ether to give 1 g of colorless needles, mp 70—72°. The IR spectrum of this product was identical with that of the sample (mp 69—71° (lit. mp 72—73°[8])) prepared by the method described by Abramov from II and diethyl phosphite. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3350 (OH), 1235 (P=O), 1060, 1035 (P–OC). *Anal.* Calcd. for $C_{10}H_{21}O_4P$: C, 50.84; H, 8.96. Found: C, 50.71; H, 8.72.

A reaction carried out in benzene with the same reagents and conditions gave the similar result.

**Ethyl (V) and Methyl 2-Oxo-cyclohexanecarboxylate (VI)**——i) A mixture of 1.5 g of II and 1.1 g of NaH (50% suspension in mineral oil) in 15 ml of benzene was refluxed for 15 hr. When cooled, 3.2 g of EDEPF was added to the mixture under stirring and ice-cooling. After stirring at the room temperature for 1 hr, the reaction mixture was poured into 2 ml of 50% $H_2SO_4$ with ice-cooling, and dried over $MgSO_4$. After evaporation of the solvent, the residue was distilled *in vacuo* to give 1 g of colorless oil (V) of bp 70—90° (1.5 mmHg) (lit. bp 125—140° (40 mmHg)[6]). IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1760 (C=O of keto-ester), 1735 (C=O of ketone), 1660 (C=O of enol-ester), 1620 (C=C of enol).

ii) The methyl ester VI was obtained by the similar manner to the above using 1 g of II, 0.7 g of NaH (50% suspension in mineral oil) and 2 g of MDEPF, bp 75—85° (2 mmHg) (lit. bp 94—95° (10 mmHg)[7]). Yield, 0.8 g. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1760 (C=O of keto-ester), 1735 (C=O of ketone), 1665 (C=O of enol-ester), 1620 (C=C of enol). NMR ($CCl_4$) $\tau$: −2.03 (singlet, *ca.* 0.5H, –OH of enol, disappeared by treatment with $D_2O$), 6.35 (singlet, 3H, –OMe), 7.50—8.90 (complex multiplet, *ca.* 8.5H, aliph. H).

**Reactions of Alkyl Dialkoxyphosphinyl Formate with NaH, $NaNH_2$, NaOEt and NaOMe**——*Materials*: EDEPF was prepared by a method reported by Warren, *et al.*,[4b] bp 113—116.5° (1 mmHg) (lit. bp 86—88 (0.25 mmHg)[4b]). MDEPF was prepared by the method reported by Reetz, *et al.*,[9] bp 87—93° (3 mmHg) (lit. bp 58—59° (1 mmHg)[9]). EDMPF was prepared from trimethyl phosphite and ethyl chloroformate by the method reported by Takamizawa, *et al.*,[10] bp 86—94° (1 mmHg) (lit. bp 124—126° (12 mmHg)[10]). MDMPF was prepared from 10 g of trimethyl phosphite and 9.2 g of methyl chloroformate by a method similar to that described by Takamizawa, *et al.*,[10] bp 81—86° (1 mmHg). Yield, 9 g. IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1740 (C=O), 1240 (P=O), 1050 (broad, P–OC). NMR ($CCl_4$) $\tau$: 6.14 (doublet, $J_{PH}$=11.0 Hz, 6H, P–O–C$\underline{H}_3$), 6.16 (doublet, $J_{PH}$=1.0 Hz, 3H, COOC$\underline{H}_3$). *Anal.* Calcd. for $C_4H_9O_5P$: C, 28.58; H, 5.40. Found: C, 28.52; H, 5.49. Sodium hydride and sodium amide were commercial reagents. Sodium ethoxide and sodium methoxide were prepared from sodium and the absolute alcohols just before use.

General Procedure: A mixture of 1 g of alkyl dialkoxyphosphinyl formate and 1.2 equiv. of a base in 8 ml of benzene was stirred under the condition shown in Table I. At the end of the reaction, 0.5 ml of 50% $H_2SO_4$ was added with chilling. After drying over 0.1 g of $MgSO_4$ for 1 hr, the benzene solution was filtered, diluted to 25 ml and analyzed by gas chromatography using an internal standard method. An authentic sample of methyl ethyl carbonate was prepared from ethyl chlorocarbonate and methanol by the method of Boehringer,[11a] bp 105—107° (lit. bp 107.2—107.3°[11b]). IR $\nu_{max}^{liq.}$ $cm^{-1}$: 1750 (C–O), 1260 (C=O). NMR ($CDCl_3$) $\tau$: 5.81 (quartet, $J$=7.5 Hz, 2H, O–$CH_2C\underline{H}_3$), 6.24 (singlet, 3H, O–C$\underline{H}_3$), 8.70 (triplet, $J$=7.5 Hz, 3H, O–$CH_2C\underline{H}_3$).

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9) T. Reetz, D.H. Chadwick, E.E. Hardy, and S. Kaufman, *J. Am. Chem. Soc.*, 77, 3813 (1955).
10) A. Takamizawa and Y. Sato, *Chem. Pharm. Bull.* (Tokyo), 12, 398 (1964).
11) *a*) C.F. Boehringer and Söhne G.M.B.H., D.R.P. 378138, *Frdl.*, 14, 141 (1926); *b*) D.F. Peppard, W.G. Brown, and W.C. Johnson, *J. Am. Chem. Soc.*, 68, 77 (1946).