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148. Akira Takamizawa, Yoshiro Sato, and Hisao Sato: Studies on Pyrimidine Derivatives and Related Compounds. XLVII.[*1] Reaction of Thiamine with Dialkyl Acylphosphonates or Methyl Phenylacylphosphinates (Takamizawa Reaction 6).

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Several kinds of dialkyl acylphosphonate (IIIa~d, Va~d) were synthesized and reacted with thiamine to give 1,6-dihydropyrimido[4',5'-4,5]pyrimido[2,3-*c*][1,4]thiazine derevatives (XIIA, B, XIIIA, B). Methyl phenylacylphosphinate also gave same result.

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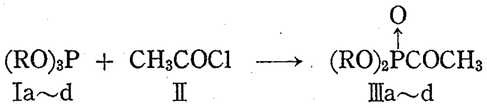
In previous papers,[*1,1)] it was reported that diethyl acetylphosphonate (IIIb) reacted with thiamine (XI) after treatment with triethylamine to give 3-(2-hydroxy)ethyl-1,4,9-trimethyl-1,6-dihydropyrimido[4',5'-4,5]pyrimido[2,3-*c*][1,4]thiazine (XIIA) and 3-(2-acetoxy)-ethyl derivative (XIIIA), with diethyl benzoylphosphonate (Vb) to give 1-phenyl-3-(2-hydroxy)ethyl-4,9-dimethyl-1,6-dihydropyrimido[4',5'-4,5]pyrimido[2,3-*c*][1,4]thiazine (XIIB) and 3-(2-benzoyloxy)ethyl derivative (XIIIB). It was also reported that treatment of XIIA, B or XIIIA, B with alkali gave corresponding 2-methyl(or phenyl)-4-(2-methyl-4-amino-5-pyrimidinyl)methyl-5-methyl-6-(2-hydroxyl)ethyl-2*H*-1,4-thiazin-3(4*H*)-one (XIVA or XIVB).

In order to examine the effect of the alkyl group of dialkyl acylphosphonate in this novel reaction, dimethyl, di-*n*-propyl, di-*n*-butyl acetylphosphonate (IIIa, IIIc, IIId), and benzoylphosphonates (Va, Vc, Vd) were synthesized, and these phosphonates reacted with XI in a similar manner. It was also found that the reactions of methyl phenylacetylphosphinate (IX)[2)] and methyl phenylbenzoylphosphinate (X) with XI gave similar results.

TABLE I.



$$\underset{\text{Ia}\sim\text{d}}{(RO)_3P} + \underset{\text{II}}{CH_3COCl} \longrightarrow \underset{\text{IIIa}\sim\text{d}}{(RO)_2\overset{\overset{O}{\uparrow}}{P}COCH_3}$$

R	b.p. (°C/mm.)	Yield (%)	Analysis (%) Calcd. C	Calcd. H	Calcd. P	Found C	Found H	Found P	IR (cm^{-1}) C=O	IR (cm^{-1}) P=O
CH_3 (IIIa)	95~96/10	68.2	31.59	5.97	20.37	31.85	6.15	20.07	1701	1268
C_2H_5 (IIIb)[2)]	113~117/19	82.8	39.99	7.27	17.20	40.21	7.29	17.60	1702	1267
n-C_3H_7 (IIIc)	84~86/1.2	48.1	46.15	8.23	14.89	46.15	8.38	14.58	1703	1264
n-O_4H_9 (IIId)	87~88/0.5	60.4	50.83	8.96	13.10	51.09	9.14	12.79	1703	1262

[*1] Part XLVI: This Bulletin, **15**, 1178 (1967).

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1) A. Takamizawa, Y. Hamashima, Y. Sato, H. Sato, S. Tanaka, H. Ito, Y. Mori: J. Org. Chem., **31**, 2951 (1966).

2) A.N. Pudovik, V.I. Nikitina, G.P. Krupnor: Zh. Obshch. Khim., **29**, 4019 (1959).

Arbuzov[3] reported the synthesis of Ⅲb. This method was applied to the syntheses of dialkyl acetylphosphonates (Ⅲa, Ⅲc, Ⅲd) from the reactions of the corresponding trialkyl phosphite (Ia, Ic, Id) and acetyl chloride (Ⅱ). Ⅲa~d were stable enough to distil, and their elemental analyses were in agreement with their compositions and showed C=O and P=O bands in infrared (IR) absorption spectra (Table I).

According to the previous report,*1 thiamine hydrochloride (Ⅺ) was treated with four moles of triethylamine in dimethylformamide (DMF) and two moles of Ⅲa~d were allowed to react, respectively. Alumina column chromatography of these reaction mixtures gave XIIIA as the crystals from the first fraction, and ⅫA was obtained as oily product from the following fraction. ⅫA was hydrolyzed to give XIVA. Results obtained here were similar to that in the case using Ⅲb (Table Ⅱ). The reaction of benzoylchloride with Ia, Ic, Id gave corresponding dialkyl benzoylphosphonates (Va,[4] Vc, Vd) (Table Ⅲ).

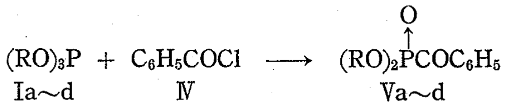
TABLE Ⅱ.

$$\text{Ⅺ} \xrightarrow[\text{in DMF}]{\text{1) 4 Et}_3\text{N} \;\; \text{2) 2 Ⅲa}\sim\text{d}} \begin{array}{c}\text{ⅫA}\\ \downarrow \\ \text{XIVA}\end{array} + \text{XIIIA}$$

R	Yield of ⅫA (%)[a]	Yield of XIIIA (%)	R	Yield of ⅫA (%)[a]	Yield of XIIIA (%)
CH_3 (Ⅲa)	21	19.2	n-C_3H_7 (Ⅲc)	24.5	30.4
C_2H_5 (Ⅲb)*1	23.6	30.4	n-C_4H_9 (Ⅲd)	23.2	26.9

a) Based on the yield of XIVA obtained from ⅫA by hydrolysis.

TABLE Ⅲ.



$$\underset{\text{Ia}\sim\text{d}}{(RO)_3P} + \underset{\text{Ⅳ}}{C_6H_5COCl} \longrightarrow \underset{\text{Va}\sim\text{d}}{(RO)_2\overset{\overset{O}{\uparrow}}{P}COC_6H_5}$$

R	b.p. (°C/mm.)	Yield (%)	Analysis (%) Calcd. C	Calcd. H	Calcd. P	Found C	Found H	Found P	IR (cm^{-1}) C=O	IR (cm^{-1}) P=O
CH_3 (Va)	108~109/0.04	78.1	50.48	5.18	14.46	50.57	5.35	14.11	1662	1267
C_2H_5 (Vb)[1]	110~112/0.12	78.2	54.55	6.24	12.80	54.22	6.37	12.68	1662	1265
n-C_3H_7 (Vc)	130~132/0.25	65.7	57.77	7.08	11.46	57.58	7.29	10.99	1662	1265
n-C_4H_9 (Vd)	131~136/0.05	62.7	60.39	7.77	10.38	60.77	7.83	10.10	1660	1258

TABLE Ⅳ.

$$\text{Ⅺ} \xrightarrow[\text{in DMF}]{\text{1) 3 Et}_3\text{N} \;\; \text{2) Va}\sim\text{d}} \text{ⅫB}$$

R	Yield of ⅫB (%)	R	Yield of ⅫB (%)
CH_3 (Va)	77.5	n-C_3H_7 (Vc)	82.3
C_2H_5 (Vb)*1	86.2[a]	n-C_4H_9 (Vd)	83.3

a) A 55.5% yield of ⅫB and a 34.1% yield of XIIIB were obtained from the reaction of 4 moles of Et_3N and 2 moles of Vb with Ⅺ.*1

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3) A. E. Arbuzov, *et al.*: Doklady Acad. Nauk S. S. S. R., **58**, 1961 (1947).

4) K. D. Berlin, H. A. Taylor: J. Am. Chem. Soc., **86**, 3862 (1962).

According to the previous report,[1] XI was treated with three moles of triethylamine in DMF and Va, Vc, and Vd were allowed to react respectively to give XIIB in good yield as well as the case of Vb (Table IV).

Next, attention was turned to alkyl phenylacylphosphinate as phosphorous compounds. Pudovik, *et al.*[2] reported the synthesis of methyl phenylacetylphosphinate (IX) from the reaction of ketene and methyl phenylhydrogenphosphonite (VII) which was derived from the reaction of dichlorophenylphosphine (VI) with methanol. However, the yield of IX was not excellent. Kamai[5] reported that dimethyl phenylphosphonite (VIII) was obtained from the reaction of VI with methanol in the presence of dimethylaniline.

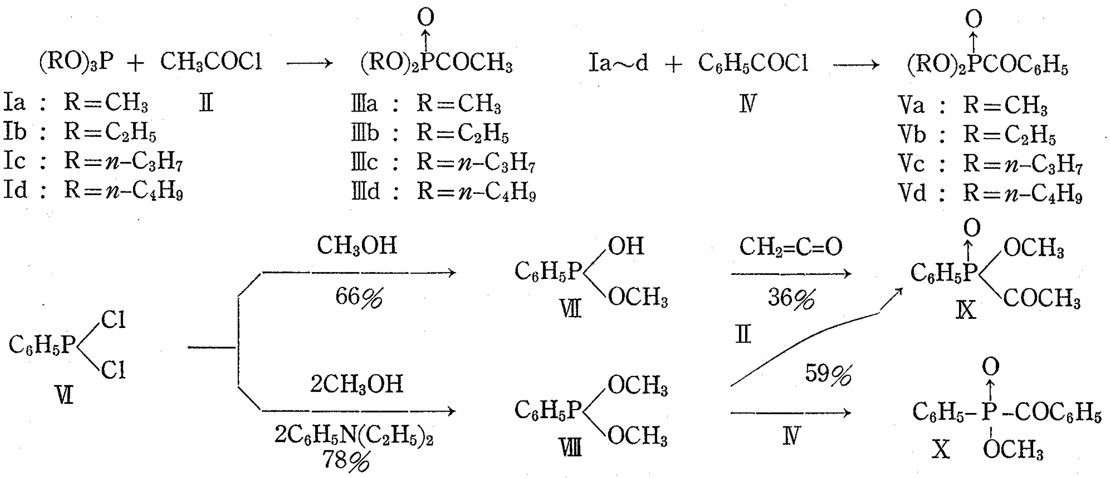

Chart 1.

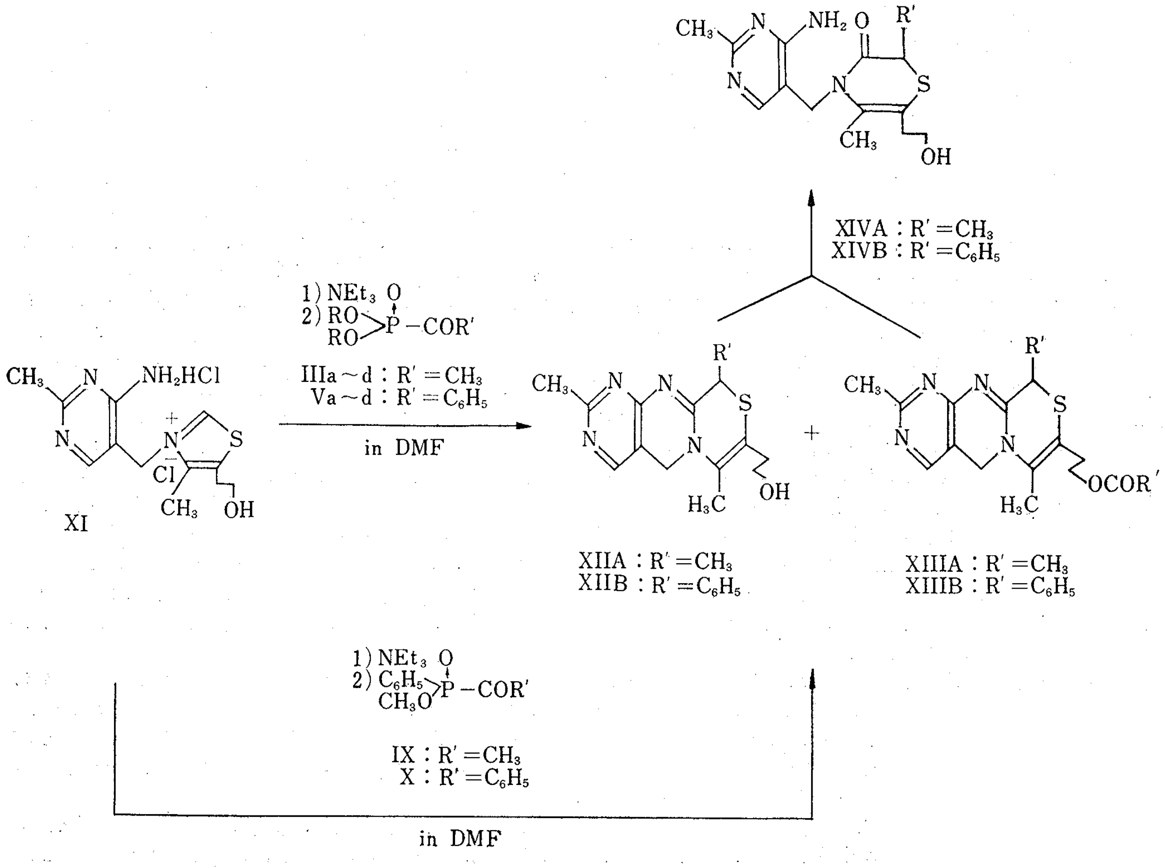

Chart 2.

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5) G. Kamai : Zh. Obshch. Khim., **18**, 443 (1948).

According to this method, Ⅵ was treated with methanol in the presence of diethylaniline to give Ⅷ in 78% yield, and then Ⅷ reacted with Ⅱ to give Ⅸ in 59% yield. The reaction of Ⅷ with Ⅳ gave methyl phenylbenzoylphosphinate (Ⅹ) as the crystals of m.p. 75~78°.

IR spectrum of Ⅹ showed the bands at 1659 (C=O), 1235 (P=O), and 1023 cm^{-1} (P-O-C). After treatment of Ⅺ with three moles of triethylamine in DMF, one equivalent of Ⅸ was allowed to react to give ⅫA as oily product. Hydrolysis of ⅫA gave XIVA in 54% yield. Similarly, after treatment of Ⅺ with four moles of triethylamine in DMF, two moles of Ⅸ was allowed to react to give ⅫA in 35.5% and XⅢA in 18.3% yield. Analogously, the reaction of one equivalent of Ⅹ with thiamine gave ⅫB in 64.4% yield, but two moles of Ⅹ afforded ⅫB in 60% and XⅢB in 27% yield. This result was comparable with the yield of 86.2% in the case using Vb.

Experimental*3

General Procedure for Preparation of Dialkyl Acetylphosphonate (IIIa~d)——Acetyl chloride (Ⅱ) was added dropwise to one equivalent of trialkyl phosphite (Ia~d) below 5° with stirring in N_2 atmosphere, and then rose slowly to room temperature during about 1 hr. The reaction mixture was distilled under reduced pressure to give dialkyl acetylphosphonate (Ⅲa~d) as a colorless oil. The data were listed in Table I.

General Procedure for Preparation of Dialkyl Benzoylphosphonate (Va~d)——Benzoyl chloride (Ⅳ) was added dropwise to one equivalent of trialkyl phosphite (Ia~d) at 10~20° with stirring in N_2 atmosphere. The temperature was risen slowly to room temperature during about 1 hr. The reaction mixture was distilled under reduced pressure to give dialkyl benzoylphosphonate (Va~d) as a yellow oil. The data were listed in Table Ⅲ.

Methyl Phenylacetylphosphinate (IX)——To a solution of 45.5 g. (0.267 mole) of dimethyl phenylphosphonite (Ⅷ) in 500 ml. of dry ether, 21.0 g. (0.268 mole) of acetyl chloride (Ⅱ) was added dropwise at −30~−40° in N_2 atmosphere. The reaction mixture was allowed to stand overnight at room temperature and distilled under reduced pressure to give 31.0 g. (58.6%) of a colorless oil, b.p.$_{0.15}$ 89.5~91°. *Anal.* Calcd. for $C_9H_{11}O_3P$: C, 54.54; H, 5.59; P, 15.62. Found: C, 54.67; H, 5.71; P, 16.07. IR ν_{max}^{film} cm^{-1}: 1698 (C=O), 1240 (P=O), 1030 (P-O-C).

Methyl Benzoylphenylphosphinate (X)——To a solution of 51.2 g. (0.301 mole) of dimethyl phenylphosphonite (Ⅷ) in 500 ml. of abs. ether, 42.0 g. (0.299 mole) of benzoyl chloride (Ⅳ) was added dropwise at −60~−70° in N_2 atmosphere. The reaction mixture was allowed to stand overnight at −5° and concentrated *in vacuo* to give 40.4 g. (52.0%) of colorless prisms, m.p. 73~75°. Recrystallization from petr. ether-ether gave colorless prisms, m.p. 76~78°. *Anal.* Calcd. for $C_{14}H_{13}O_3P$: C, 64.62; H, 5.04; P, 11.91. Found: C, 64.49; H, 5.14; P, 11.66. IR ν_{max}^{Nujol} cm^{-1}: 1659 (C=O), 1235 (P=O), 1023 (P-O-C).

3-(2-Hydroxy)ethyl-1,4,9-trimethyl-1,6-dihydropyrimido[4′,5′-4,5]pyrimido[2,3-*c*][1,4]thiazine (XIIA) and 3-(2-Acetoxy)ethyl-1,4,9-trimethyl-1,6-dihydropyrimido[4′,5′-4,5]pyrimido[2,3-*c*][1,4]thiazine (XIIIA)——a) To a suspension of 5.0 g. (0.0148 mole) of Ⅺ (dried over P_2O_5 at 110° *in vacuum*) in 25 ml. of DMF, 6.0 g. (0.0593 mole) of triethylamine was added dropwise below 10°. The reaction mixture was stirred for 1 hr. with cooling and 0.0296 mole of dialkyl acetylphosphonate (Ⅲa~d) was added dropwise. After stirred for about 1 hr. with cooling until heat generation ceased, stirring was continued for 2~3 hr. at room temperature. The reaction mixture was allowed to stand overnight at room temperature and then heated at 70~80° for 4 hr. After removal of DMF *in vacuo*, the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with *N*-$NaHCO_3$, dried over Na_2SO_4, and evaporated. The residual oil was dissolved in AcOEt and chromatographed on alumina. Elution with AcOEt gave yellow crystals, which were recrystallized from ether-AcOEt to give XⅢA as yellow needles, m.p. 120~123° (decomp.). UV λ_{max}^{EtOH} mμ (ε): 371 (10680). *Anal.* Calcd. for $C_{16}H_{20}O_2N_4S$: C, 57.81; H, 6.06; N, 16.86; S, 9.65; O, 9.63. Found: C, 58.00; H, 6.27; N, 17.17; S, 9.76; O, 9.77.

Further elution with AcOEt gave ⅫA as an orange oil, which was heated with 5% KOH in MeOH at 60° for 2 hr. After removal of MeOH, the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and evaporated to leave an oil, which was crystallized with ether and recrystallized from EtOH to give XIVA as colorless needles, m.p. 159~161° (decomp.). Identity was confirmed by IR comparison with an authentic sample.*1 Yields were listed in Table Ⅱ.

b) To a suspension of 10.1 g. (0.03 mole) of dried Ⅺ in 50 ml. of DMF, 9.1 g. (0.09 mole) of triethylamine was added dropwise and stirred for 1 hr. below 10°. To this suspension, 6.0 g. (0.03 mole) of Ⅸ was added dropwise below 5° and then rose to room temperature slowly. After standing overnight at room temperature,

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*3 Melting points and boiling points are uncorrected.

DMF was removed *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with dil. $NaHCO_3$, dried over Na_2SO_4, and evaporated. The residual oil was refluxed with 100 g. of 5% KOH–MeOH at 60° for 1.5 hr. The reaction mixture was concentrated *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and evaporated. The residue was crystallized with ether to give 5.02 g. (54.2%) of XIVa, m.p. 147~151° (decomp.). Identity was confirmed by IR comparison with an authentic sample.

c) To a suspension of 5 g. (0.0148 mole) of dried XI in 25 ml. of DMF, 6 g. (0.0594 mole) of triethylamine was added dropwise below 6° and stirred for 1 hr. To this suspension, 5.9 g. (0.0298 mole) of IX was added dropwise below 5° and stirred for 1 hr. at 3° and for 5 hr. at room temperature. After standing overnight at room temperature, stirred at 73° for 4 hr. DMF was removed *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was worked up as described above a) and alumina chromatography gave 0.9 g. (18.3%) of XIIIA, m.p. 120~122° (decomp.), and XIIA as an oil, which was hydrolyzed to give 1.62 g. (35.5%) of XIVA. These compounds were proved to be identical with authentic samples by IR comparison.

1-Phenyl-3-(2-hydroxy)ethyl-4,9-dimethyl-1,6-dihydropyrimido[4′,5′-4,5]pyrimido[2,3-*c*][1,4]thiazine (XIIB) and 1-Phenyl-3-(2-benzoyloxy)ethyl-4,9-dimethyl-1,6-dihydropyrimido[4′,5′-4,5]pyrimido[2,3-*c*]-[1,4]thiazine (XIIIB)——a) To a suspension of 10.1 g. (0.03 mole) of XI (dried over P_2O_5 at 110° *in vacuum*) in 50 ml. of DMF, 9.1 g. (0.09 mole) of triethylamine was added dropwise below 10° and stirred for 1 hr. with cooling. Dialkyl benzoylphosphonate (Va~d) (0.03 mole) was added dropwise and stirred for 30 min. below 10° and then for 2~3 hr. at room temperature. After the reaction mixture was allowed to stand overnight at room temperature, the solvent was removed *in vacuo* at 40° and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with *N*-$NaHCO_3$, dried over Na_2SO_4, and evaporated. The residual oil was crystallized with ether to give XIIB as yellow crystals, which were recrystallized from MeOH to give yellow needles, m.p. 204~206°. Identity with an authentic sample[1] was confirmed by IR comparison. Yields were listed in Table IV.

b) To a suspension of 10.1 g. (0.03 mole) of dried XI in 50 ml. of DMF, 9.1 g. (0.09 mole) of triethylamine was added dropwise and then 7.8 g. (0.03 mole) of X was added dropwise at 2°. The reaction mixture was worked up as described above to give 6.8 g. (64.4%) of XIIB, m.p. 199~201°, which was proved to be identical with an authentic sample by IR comparison.

c) To a suspension of 6.7 g. (0.0199 mole) of XI in 45 ml. of DMF, 8.1 g. (0.081 mole) of triethylamine was added at 8° and stirred for 1 hr. To this suspension, 10.4 g. (0.04 mole) of X was added and stirred for 20 min. at 3°, for 6.5 hr. at room temperature, and then 4 hr. at 75°. DMF was removed *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with dil. $NaHCO_3$, dried over Na_2SO_4, and evaporated. The residual crystals were chromatographed on alumina (neutral) with AcOEt to give 2.64 g. (27.1%) of XIIIB, m.p. 191~194° (decomp.) and 4.24 g. (60.5%) of XIIB, m.p. 199~201°. These compounds were identified with authentic samples by IR comparison.

The authors are indebted to the member of the analytical section of this laboratory for elemental analyses.