Dehydrooligopeptides. VI. Facile Transformation of α-Phosphoranylideneamino-α-alkenoates to Δ^2-Dehydrodipeptide Derivatives[1)]

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Synopsis. Arbusov reaction of alkyl α-phosphoranylideneamino-α-alkenoates with several halides gave the corresponding α-phosphinylamino-α-alkenoates and Δ^2-dehydrodipeptide derivatives.

In connection with the synthesis of α-dehydroamino acids (DHAs) and dehydropeptides (DHPs), we briefly reported that the an Arbusov-type reaction of alkyl 2-triethoxyphosphoranylideneamino-2-alkenoates (**2**) gave the corresponding diethoxyphosphinyl (Dep) derivatives and that a similar reaction of **2** with phthaloyl (Pht)–Leu–Cl also gave Pht-(Dep)-Δ^2-dehydrodipeptide derivatives.[2-4)]

This paper deals with the utilization of **2** and alkyl 2-triphenylphosphoranylideneamino-2-alkenoates (**3**),[2)] derived from alkyl (*Z*)-2-azido-2-alkenoates (**1**) and $P(OEt)_3$ or $P(C_6H_5)_3$ respectively, to the synthesis of DHA and DHP derivatives. In order to further extend the reaction of **2** and **3**, we chose several halides, including Pht-(L)-α-amino acid (AA) chlorides as reagents.

According to the method reported,[3)] a similar reaction of (*Z*)-**2** with chloroacetyl chloride gave alkyl 2-(*N*-chloroacetyl)-2-diethoxyphosphinylamino-2-alkenoates (**5**). From the results, it was found that after an addition of acyl chloride to the N=P bond of **2** (**4**), an Arbusov reaction of **4** immediately took place, giving **5**, as is illustrated in Scheme 1.

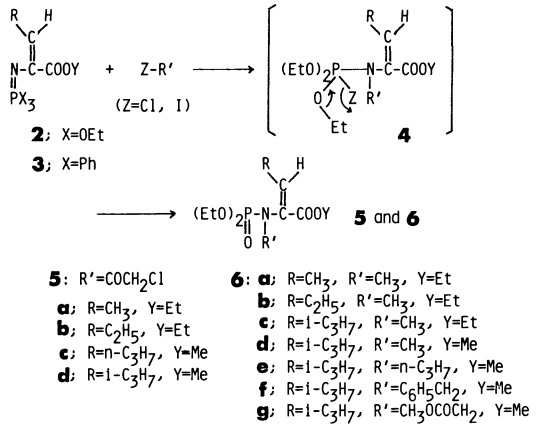
Furthermore, when **2** was treated with alkyl iodide or methyl iodoacetate, a similar reaction readily proceeded to give alkyl 2-[*N*-(alkyl)diethoxyphosphinylamino]-2-alkenoates (**6**). As a result, alkyl halides as well as acyl chlorides were found to be sensitive to the 2-triethoxyphosphoranylideneamino function. In addition, a reaction of **2** with Pht–Gly–Cl or Pht-(L)-Leu–Cl was attempted under similar conditions as those mentioned above to give the expected Pht-(Dep)-Δ^2-(L,Z)-dehydrodipeptide esters (**7** and **8**).

Subsequent treatments of **7** and **8**, respectively, with 25% HBr in acetic acid gave deblocked Pht-Δ^2-(L,Z)-dehydrodipeptide esters (**9** and **10**). However, it was found that the other deprotection of **7** and **8** with HCl in MeOH, HCl in benzene, and with CF_3COOH, respectively, did not take place, even under heating. On the other hand, interestingly, a treatment of **3** with Pht–Gly–Cl in benzene under reflux, and then that of the resulting solution with $NaHCO_3$ aqueous solution, directly gave **9**; however, a similar reaction of **2** did not proceed. Moreover, even a one-pot reaction of **1** with Pht–Gly–Cl and $P(C_6H_5)_3$, **9** was also obtained (see Scheme 2). The results, thus obtained, are summarized in Tables 1—4.

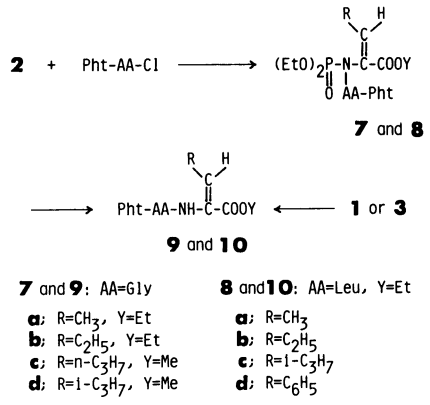
Table 1. Properties of Products (**5** and **6**)

Compd[a)] No.	Yield %	Bp[b)] (θ_b/°C)mmHg[c)]	^{1}H NMR (δ) -CH= (*J*, Hz)
5a	60	Syrup	7.16 dq (2.0, 7.0)
5b	80	Syrup	7.02 dt (2.0, 7.0)
5c	73	Syrup	7.04 dt (2.0, 7.0)
5d	75	Syrup	6.84 dd (1.9, 11.0)
6a	95	98—100/0.14	7.06 dq (2.1, 7.0)
6b	90	108—110/0.09	6.80 dt (2.1, 7.0)
6c	92	110—112/0.08	6.63 dd (2.0, 10.5)
6d	92	102—104/0.09	6.62 dd (2.0, 10.5)
6e	90	120—125/0.05	6.60 dd (2.0, 10.5)
6f	88	Syrup	6.52 dd (2.0, 11.0)
6g	86	Syrup	6.70 dd (2.0, 11.0)

a) All the compounds were analyzed for C, H and N and gave analytical values within 0.3% of the theoretical ones. b) Colorless. c) 1 mmHg = 133.322 Pa.



Scheme 1.



Scheme 2.

Table 2. Properties of Products (**7** and **8**)

Compd[a] No.	Yield %	Mp[b] θ_m/°C	^{1}H NMR (δ) -CH= (J,Hz)	$[\alpha]_D^{25}$ (c 0.2)[c]
7a	70	61—62	7.20 dd (2.0, 7.0)	
7b	67	99—100	7.06 dt (2.0, 7.0)	
7c	83	89—90	7.10 dt (2.0, 7.0)	
7d	74	98—99	6.90 dd (2.0, 11.0)	
8a	70	59—60	7.02 dq (2.0, 7.0)	−21.5°
8b	66	79—80.5	6.90 dt (2.0, 7.0)	−60.2°
8c	64	Syrup	6.75 dd (2.2, 11.0)	−45.3°
8d	60	119—120	7.35— 7.84m (C_6H_5+H)	−40.4°

a) See footnote a) in Table 1. b) Colorless prisms from cyclohexane. c) Measured in methanol.

Table 3. Yields of **9** from **1**, **3**, and **7**

Compd. No.	From **1**	From **3**	From **7**	Mp(θ_m/°C[a])
9a	48	51	97	177—179 (180.5—181.5[b])
9b	43	50	86	173—175 (173—173.5[b])
9c	43	48	72	174—175[c]
9d	41	45	71	164—165 (162—165[b])

a) Colorless needles. b) Lit,[5]. c) See footnote a) in Table 1.

Based on the spectral data as well as a satisfactory elemental analysis, the structures of all the new compounds could be readily determined. The NMR spectra of the products showed long-range coupling between β-olefinic, γ-methyl or γ-methylene protons and the phosphorus atom. In the case of **6**, in addition to the above long-range couplings, another coupling between *N*-alkyl protons and phosphorus also appeared.

As is summarized in the Tables, the characteristic olefin proton signals of **6** shifted at the δ 7.06—6.52 ($J_{3,4}$=7.0—11.0 Hz) region, whereas those of **5**, **7**, and **8** resonated at a slightly lower magnetic field at the δ 7.60—6.75 region with a similar coupling constant ($J_{3,4}$=7.0—11.0). On the other hand, the coupling constants between the β-olefinic proton and phosphorus in **6** were also found to be almost the same ($J_{3,P}$=1.9—2.2 Hz) as that of **5**, **7**, and **8**. In addition, the methyl and methylene protons at the nitrogen coupled with phosphorus and was observed as a doublet (J=7.5—10.0 Hz). Consequently, all the signals and the coupling constants of the new compounds obtained could be assigned.

Furthermore, in the IR spectrum of the products, the characteristic absorption bands of ester carbonyl, C=C, -P=O, and =P-O-CH_2- functions appear at 1715—1760 (strong; s), 1615—1660 (medium), 1260—1280 (s), and 1020—1040 (s) cm^{-1}, respectively.

In closing, since **9** was in accordance with the authentic samples[5] and **10** was prepared independently by a reaction of Pht-(L)-Leu-Cl with ethyl 2-amino-2-alkenoates or *N*-carboxy α-dehydroamino acid anhydrides,[6] the structures could be readily determined as alkyl 2-phthaloylglycyl-and-(L)-leucyl-amino-2-alkenoates, respectively.

Table 4. Properties of Products (**10**)

Compd[a] No.	Yield %	Mp[b] θ_m/°C	^{1}H NMR (δ) -CH= (J, Hz)	$[\alpha]_D^{25}$ (c 0.2)[c]
10a	60	90—91	6.54 d (8.0)	−20.2°
10b	60	169—170	6.44 d (8.0)	−52.5°
10c	55	117—119	6.41 d (10.0)	−55.8°
10d	65	164—165	7.22— 7.50m (Ph+H)	−49.6°

a) See footnote a) in Table 1. b) Colorless needles from ethyl acetate and cyclohexane. c) Measured in methanol.

Experimental

All the boiling and melting points are uncorrected. The IR spectra were recorded with a Hitachi EPI-G3 spectrometer. The NMR spectra were measured with a JEOL JNM-PS-100 spectrometer in a $CDCl_3$ solution with tetramethylsilane as the internal standard.

Preparation of 5. To a solution of **2** (25 mmol) in dry benzene (30 ml) was added chloroacetyl chloride (50 ml) with stirring under cooling. The resulting solution was continuously stirred at room temperature for 2.5 h. After removing the solvent, the obtained residual syrup was purified on a silica-gel column using a mixture of benzene–ethyl acetate (4:1 v/v) as the eluent to give **5**.

Preparation of 6. A reaction of **2** (15 mmol) with an appropriate alkyl iodide or methyl iodoacetate (45 mmol) was similarly worked up under reflux for 4 h to give a residual syrup, which was distilled in vacuo or purified on a silica-gel column using a mixture of benzene–ethyl acetate (5:1 v/v) as the eluent to give **6**.

Preparation of 7 and 8. A treatment of **2** (10 mmol) with Pht-(L)-AA-Cl (11 mmol) was similarly worked up at room temperature for 12 h to give a reaction solution which was washed with saturated $NaHCO_3$ solution and water and then dried over anhydrous Na_2SO_4. The removal of the solvent under reduced pressure gave a crude syrup, which was purified on a silica-gel column using a mixture of benzene–ethyl acetate (4:1 v/v) as the eluent to give **7** and **8** as a syrup or crystals.

Preparation of 9. a) A solution of **7** (3 mmol) in 25% HBr in acetic acid (5 ml) was stirred at room temperature for 3h and then the excess solvent was removed to give crystals. Recrystallization from EtOH gave **9**.

In a similar manner, a treatment of **8** with 25% HBr in acetic acid was worked up to give **10**.

b) A solution of an equimolar **3** (10 mmol) and Pht-Gly-Cl in dry benzene (30 ml) was refluxed for 5 h. The resulting solution was washed five times with a saturated $NaHCO_3$ solution and then three times with water and finally dried over anhydrous Na_2SO_4. The removal of the solvent gave residual crystals, which were recrystallized from EtOH to give **9**.

c) Into a solution of **1** (10 mmol) in dry benzene (30 ml) $P(C_6H_5)_3$ (10 mmol) was added with stirring, portionwise, under cooling. After stirring at room temperature for 1 h, Pht-Gly-Cl (10 mmol) was added to the

resulting solution and then refluxed for 5 h. Finally, the reaction solution was similarly worked up to give **9**.

References

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6) Unpublished data.