α,β-Unsaturated Carboxylic Acid Derivatives. XXI. A Novel Synthesis of α-Dehydroamino Acid Derivatives by the Arbusov Reaction of α-Phosphoranylideneamino-2-alkenoates[1]

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The reaction of ethyl 2-azido-2-alkenoate with organic tervalent phosphorus reagent gave the corresponding 2-phosphoranylideneamino derivative as an stable intermediate. This transformed gradually at room temperature, or immediately on a silica-gel column to give the corresponding 2-phosphinylamino derivative in a good yield. The Arbusov reaction of the intermediate which occurred during the transformation was found to be applicable for the other azido olefins. The formation mechanism and the configurational determination of the new products are discussed.

In connection with the synthesis of α-dehydroamino acid (DHA), which is an important constituent or precursor in the versatile cyclic peptide antibiotics, the development of the synthetic methods for DHA has been of interest and several routes have been investigated by us.[2-6]

So far, no report has been appeared on the synthesis of DHA N-protected with phosphinyl group except for our earlier paper,[7] whereas the diphenylphosphinyl (Dpp) group was utilized recently as an useful N-protecting group for α-amino acid and peptide.[8,9]

In the present paper, we wish to report a preparative route for DHA N-protected with a few kinds of phosphinyl groups by the reaction of ethyl 2-azido-2-alkenoate (**1**) with organic tervalent phosphorus reagents by two steps. Furthermore, the attempt to employ a similar reaction of *t*-butyl 3-azido-2-acetylamino-2-alkenoate (**8**) with triethyl phosphite was successful in giving the corresponding β-N-phosphinyl-DHA derivative.

Results and Discussion

*Reaction of **1** with Tervalent Phosphorus Reagent.* The reaction of (*Z*)-isomer of **1** (**a**; R=CH_3, **b**; R=C_2H_5, **c**; R=*n*-C_3H_7, **d**; R=*i*-C_3H_7, **e**; R=C_6H_5) with equimolar triphenylphosphine as a typical organic tervalent phosphorus reagent in dry benzene under nitrogen gas at room temperature was readily carried out to give colorless crystals or a syrup, which was identified as ethyl 2-triphenylphosphoranylideneamino-2-alkenoate (**2**), obtained in *ca.* 80% yield. The compound **2** thus obtained was found to be a very stable, even though it was heated for a long time or treated with an acid or a base.

In a similar manner, the reaction of **1** with triethyl phosphite also proceeded smoothly to give a colorless viscous oil, which was identified as 2-triethoxyphosphoranylideneamino-2-alkenoate (**3**), in *ca.* 81% yield. However, the syrupy product **3** isolated purely by the vacuum distillation was found to change gradually into a yellowish solid substance at room temperature during about a month. The colorless crystals obtained in *ca.* 87% yield from **3** were characterized to be ethyl 2-diethoxyphosphinylamino-2-alkenoate (**4**). Interestingly, when the chromatogram of **3** was developed through a silica-gel column using benzene initially and then a mixture of benzene–ethyl acetate (6 : 1 v/v) as the eluent, the compound **3** immediately transformed to give **4** in a fairly good yield. Since the transformation of **3** to **4** was further promoted in the presence of water, it was found that **3** reacted with water to give **4**. As a result, the desired new DHA N-protected with phosphinyl group was first synthesized.

Furthermore, in order to ascertain and generalize the preparative route for the DHA N-protected with phosphinyl group from **1**, a similar reaction of **1** with ethyl diphenylphosphinite was also performed to obtain ethyl 2-ethoxydiphenylphosphoranylideneamino-2-alkenoate (**5**) as a colorless syrup in an almost quantitative yield. Subsequently, the treatment of **5** on a silica-gel column was worked up similarly to give the expected ethyl 2-diphenylphosphinylamino-2-alkenoate (**6**) as colorless needles in *ca.* 74% yield. Furthermore, in order to remove the Dpp N-protecting group, when ethyl 2-diphenylphosphinylamino-2-butenoate (**6a**) was treated with trifluoroacetic acid at room temperature for 2 h, ethyl 2-trifluoroacetylamino-2-butenoate (**7a**) was readily obtained in 75% yield. The structure of **7a** was determined by the independent preparation from ethyl (*Z*)-2-amino-2-butenoate and trifluoroacetic anhydride. Since Breitholle and Stammer[10] reported the removal of N-trifluoroacetyl group in DHA and dehydropeptide (DHP) with amine, the Dpp group was found to be a useful N-protecting group for DHA and DHP, although two-step treatments were required.

In order to confirm the structure and the configuration of **2**—**5**, and **6** thus obtained, the independent preparation of **4** was performed. The reaction of (*Z*)-isomer of ethyl 2-amino-2-alkenoate with diethyl phosphorochloridate by the usual method proceeded to give colorless crystals, whose properties were in complete agreement with **4** prepared from (*Z*)-**1** and triethyl phosphite *via* **3**. As a result, the geometric structure of **4** and **6** could be easily determined to be (*Z*)-isomerism. Accordingly, the configurational structure of **2**, **3**, and **5** was also assigned to be (*Z*)-geometry. On the other hand, the attempt to obtain another independent

preparation of **4** by the direct condensation of α-oxo carboxylic acid ester with diethyl phosphoramidate by the method reported previously[6] was unsuccessful, because of the lability and the decomposition of the phosphoramidate in acidic conditions.

The structure and configuration confirmed above were further supported by the results of the following spectroscopic analyses and by the studies on the formation mechanism.

In the IR spectrum of **2**, **3**, and **5**, the characteristic absorption bands of ester carbonyl, carbon-carbon double bond, and =P–O–CH_2– groups appear at 1722—1700 (strong), 1630—1590 (medium), and 1050—1035 (in **3** and **5**, strong) cm^{-1} regions respectively. On the other hand, in that of **4** and **6**, the stretching absorption bands of NH and >P=O groups newly appear at 3170—3070 (medium) and 1290—1240 (strong) cm^{-1} regions, along with the appearance of ethoxycarbonyl and C=C bands at 1730—1710 and 1660—1625 cm^{-1} regions, respectively.

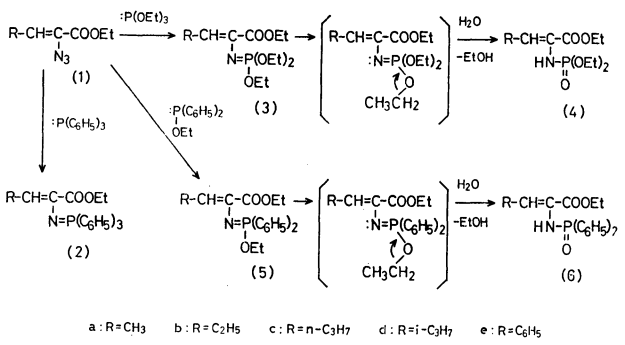
On the other hand, the NMR spectra of **2**—**5**, and **6**, clearly showed the long range coupling between β-olefinic, γ-methylene protons, and phosphorus atoms. As summarized in Tables 1 and 2, the olefinic proton signals of **2**, **3**, and **5** shifted at δ 6.70—5.95 ($J_{3,4}$= 6.8—9.2 Hz), whereas those of **4** and **6** resonated at lower magnetic field (at δ 7.23—6.02) with the comparatively larger coupling constant ($J_{3,4}$=7.0—11.4 Hz). On the other hand, the coupling constants between β-olefinic proton and phosphorus in **4** and **6** were found to be smaller ($J_{3,P}$=1.8—2.6 Hz) than the constants ($J_{3,P}$=2.9—4.5 Hz) in **2**, **3**, and **5**. Similarly, the long range coupling between γ-methylene protons and phosphorus ($J_{4,P}$=2.5—3.0 Hz) was also observed, as listed in Tables 1 and 2. Moreover, in the NMR and IR spectra of **4** and **6**, the appearance of NH groups at δ 5.50—4.70 and at *ca.* 3100 cm^{-1} respectively indicates unambiguously the transformation of the phosphoranylideneamino into the phosphinylamino group.

The above results suggest the following formation mechanism of **4** and **6**: the Arbusov reaction of the intermediates **3** and **5** with water occurred to give **4** and **6** respectively, along with the yielding of ethanol, which could be detected by gas chromatography. This process is illustrated in Scheme 1.

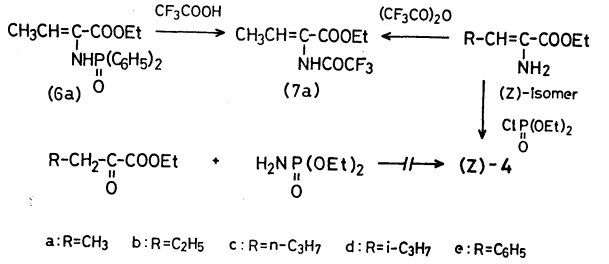
The yields, physical constants, and NMR spectral data of **2**—**5**, and **6** are summarized in Tables 1 and 2.

Reaction of 8 with Triethyl Phosphite. In order to apply extensively to the various azido olefins, β-azido olefin was subjected to the reaction with triethyl phosphite.

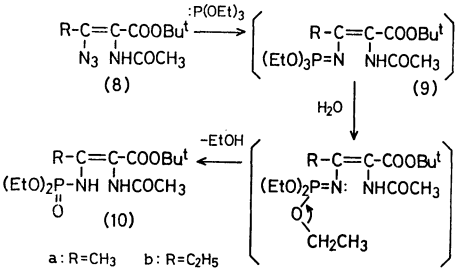
As in the case of **1**, *t*-butyl 2-acetylamino-3-azido-2-alkenoate (**8**: **a**; R=CH_3, **b**; R=C_2H_5), derived by the reaction of *t*-butyl 2-(*N*-bromoacetylamino)-2-alkenoate with sodium azide, with the successive substitution and the subsequent 1,3-shift,[11] was treated with triethyl phosphite to give a pale yellowish syrup in a fairly good yield. Interestingly, the syrupy products thus obtained were found to have a satisfactory elemental analysis for the corresponding β-phosphinylamino derivative (**10**), not the expected β-phosphoranylideneamino derivative (**9**). Furthermore, the above structural identification



Scheme 1.



Scheme 2.



Scheme 3.

was exactly supported by the IR and NMR spectral data as follows. The appearance of the absorption band at 3260—3200 cm^{-1} and that of the chemical shift resonating at δ 6.83—6.70 regions as a broad singlet due to NH and the presence of >P=O at 1260 cm^{-1} as a strong absorption indicates unambiguously the formation of an α,β-unsaturated α,β-diamino derivative, which was identified as *t*-butyl 2-acetylamino-3-diethoxyphosphinylamino-2-alkenoate, obtained in *ca.* 78% yield.

The above results show that the formation mechanism of **10** was the following: the one-pot reaction of **8** with triethyl phosphite took place to give the unstable intermediate **9**, then the following Arbusov reaction with water during the treatment process gave **10**, as is illustrated in Scheme 3.

Experimental

All the melting and boiling points are uncorrected. The IR spectra were recorded with a Hitachi EPI-G3 Spectrometer. The NMR spectra were measured with a JNM-PS-100 Spectrometer (Japan Electron Laboratory Co. Ltd.), using tetramethylsilane as the internal standard.

Preparation of 2. Into a solution of (*Z*)-**1** (50 mmol) in dry benzene (50 ml) under nitrogen gas we stirred triphenyl-

Table 1. Ethyl (*Z*)-2-phosphoranylideneamino-2-alkenoate (**2**, **3**, and **5**)

Compd No.	Yield %	Bp/°C[mmHg] (Mp/°C)[a]	Formula	Found (Calcd) (%) C	H	N	NMR spectrum, δ in $CDCl_3$ Olefinic proton (J_{Hz})	γ-Proton (J_{Hz})
2a	72	(101—102)	$C_{24}H_{24}NO_2P$	74.12 (74.04	6.21 6.17	3.56 3.60)	6.04dt (3.0) (7.0)	
2b	87	syrup	$C_{25}H_{26}NO_2P$	74.56 (74.44	6.58 6.45	3.25 3.47)	5.95dt (2.9) (6.9)	
2c	91	syrup	$C_{26}H_{28}NO_2P$	74.88 (74.82	6.98 6.71	3.28 3.36)	5.98dt (3.0) (8.3)	
2d	68	(71—72)	$C_{26}H_{28}NO_2P$	74.92 (74.82	6.81 6.71	3.34 3.36)	5.82dd (3.0) (8.3)	
2e	85	(141—142)	$C_{29}H_{26}NO_2P$	77.20 (77.16	7.49 7.47	3.05 3.10)	6.78d (6.8)	
3a	83	105—107/[0.5]	$C_{12}H_{24}NO_5P$	49.81 (49.14	8.71 8.25	4.21 4.78)	5.99dq (4.0) (6.9)	1.79dd (3.0) (6.9)
3b	63	111—115/[0.5]	$C_{13}H_{26}NO_5P$	51.15 (50.80	8.84 8.53	4.71 4.56	5.92dt (4.1) (7.0)	2.29dq (2.7) (7.0)
3c	92	113—115/[0.5]	$C_{14}H_{28}NO_5P$	52.45 (52.32	8.85 8.78	4.41 4.36)	5.93dt (4.1) (7.0)	2.28dq (2.7) (7.0)
3d	75	115—119/[0.5]	$C_{14}H_{28}NO_5P$	52.39 (52.32	8.82 8.82	4.39 4.39)	5.77dt (4.5) (8.3)	2.97m
3e	89	syrup	$C_{17}H_{26}NO_5P$	57.95 (57.95	7.03 7.03	3.58 3.58)	6.70d (8.0)	7.12—7.36m (C_6H_5+H)
5a	91	syrup	$C_{20}H_{24}NO_3P$	67.33 (67.21	6.76 6.77	3.68 3.92)	6.18dq (4.0) (7.0)	2.02dd (2.5) (7.0)
5b	90	syrup	$C_{21}H_{26}NO_3P$	67.85 (67.91	7.00 7.06	3.91 3.77)	6.08dt (4.0) (7.2)	2.56dq (2.5) (7.2)
5c	89	syrup	$C_{22}H_{28}NO_3P$	69.05 (68.55	7.09 7.32	3.48 3.64)	6.10dt (4.0) (7.2)	2.52dq (2.5) (7.2)
5d	90	syrup	$C_{22}H_{28}NO_3P$	68.79 (68.55	7.38 7.32	3.49 3.64)	5.94dd (4.5) (9.2)	3.24m
5e	85	syrup	$C_{25}H_{26}NO_3P$	71.52 (71.58	6.29 6.25	3.31 3.34)	6.80d (6.8)	7.16—8.20 (C_6H_5+H)

a) Colorless needles from cyclohexane.

Table 2. Ethyl (*Z*)-2-phosphinylamino-2-alkenoates (**4** and **6**)

Compd No.	Yield/% A[a]	B[b]	Mp/°C[c]	Formula	Found (Calcd) (%) C	H	N	NMR spectrum, δ in $CDCl_3$ Olefinic proton (J_{Hz})	γ-Proton(J_{Hz})	NH(J_{Hz})
4a	87	81	47—48	$C_{10}H_{20}NO_5P$	45.22 (45.22	7.63 7.63	5.25 5.24)	6.50dq (2.6) (7.0)	1.92dd (2.6) (7.0)	4.78
4b	86	81	30—31	$C_{11}H_{22}NO_5P$	47.39 (47.30	7.91 7.94	5.11 5.02)	6.37dt (2.6) (7.0)	2.42dq (2.6) (7.0)	4.80
4c	81	76	46—47	$C_{12}H_{24}NO_5P$	49.20 (49.14	8.21 8.25	4.77 4.78)	6.42dt (2.6) (7.0)	2.39dq (2.6) (7.0)	4.78
4d	88	71	40—42	$C_{12}H_{24}NO_5P$	49.11 (49.14	8.28 8.25	4.71 4.78)	6.19dd (2.5) (10.0)	3.06m	4.70
4e	91		70—71	$C_{15}H_{22}NO_5P$	55.01 (55.04	6.75 6.78	4.32 4.28)	7.23s	7.36—7.77m (C_6H_5+H)	4.80
6a	70		121—122	$C_{18}H_{20}NO_3P$	65.69 (65.64	6.05 6.12	4.22 4.25)	6.36dq (2.1) (8.0)	1.84d (8.0)	5.50d (8.0)
6b	77		85—85.5	$C_{19}H_{22}NO_3P$	66.41 (66.46	6.45 6.46	4.03 4.08)	6.24dt (2.0) (8.0)	2.40qu (8.0)	5.50d (8.0)
6c	68		97—98	$C_{20}H_{24}NO_3P$	67.28 (67.21	6.79 6.77	3.85 3.92)	6.20dt (2.0) (8.0)	2.34q (8.0)	5.48d (8.0)
6d	65		106—107	$C_{20}H_{24}NO_3P$	67.23 (67.21	6.71 6.77	3.81 3.92)	6.02dd (1.8) (11.4)	3.32m	5.41d (8.6)
6e	89		168—169	$C_{23}H_{22}NO_3P$	70.69 (70.62	5.73 5.67	3.66 3.58)	7.00s	7.18—7.78m (C_6H_5+H)	5.38d (6.0)

a) From **3** and **5**. b) From ethyl (*Z*)-2-amino-2-alkenoate and $ClP(O)(OEt)_2$. c) Colorless needles from cyclohexane.

phosphine (50 mmol), portion by portion, under cooling. After the resulting solution had been stirred at room temperature for 1 h, the benzene was evaporated under reduced pressure to give a colorless syrup or a semi-solid residue, in which the latter was crystallized in petroleum ether (20 ml). The collected crystals were recrystallized from cyclohexane to give colorless needles.

Preparation of ***3***. A solution of equimolar (*Z*)-**1** (50 mmol) and triethyl phosphite in dry benzene was worked up similarly to give an oily residue, which was distilled under reduced pressure to give a colorless viscous oil.

Preparation of ***5***. A solution of equimolar (*Z*)-**1** (50 mmol) and ethyl diphenylphosphinite in dry benzene was worked up similarly for 3 h to give a colorless syrup.

Preparation of ***4***. *From* ***3***. *By Standing*: When viscous oil (**3**) was allowed to stand at room temperature for about a month, the oil gradually crystallized to give a yellowish solid substance. The collected solid was recrystallized from hexane or cyclohexane to give colorless needles.

On a Silica-gel Column. The compound **3** (50 mmol) was chromatographed on a silica-gel column using benzene (150 ml) intially and then a mixture of benzene–ethyl acetate (6 : 1 v/v) as the eluent. The fraction solution obtained was evaporated under reduced pressure to give colorless crystals.

From Ethyl (Z)-2-Amino-2-alkenoate and $ClP(O)(EtO)_2$. Into a solution of the enamine (20 mmol) and pyridine (30 mmol) in dry diethyl ether (30 ml) we stirred diethyl phosphorochloridate (25 mmol), drop by drop, at room temperature. After the resulting solution had been stirred at room temperature for 5 h, ether (50 ml) was further added to the reaction solution and then the resultant solution was washed with 1 M HCl†† and with water three times. The ether layer was dried over anhydrous Na_2SO_4 and then concentrated to give a residual product. The residue was purified on a silica-gel column using ehter as the eluent to give colorless needles, which was in agreement with **4** obtained above. Yield *ca.* 80%.

Preparation of ***6***. In a similar manner to that in the case of **4**, compound **5** was chromatographed on a silica-gel column using a mixture of benzene and ethyl acetate (4 : 1 v/v) as the eluent. The fraction obtained was condensed under reduced pressure to give crude residual crystals, which were collected by filtration and then recrystallized from cyclohexane to give **6** as colorless needles.

Preparation of ***7a***. *From* ***6a*** *and* CF_3COOH: A solution of **6a** (10 mmol) in trifluoroacetic acid (5 ml) was stirred at room temperature for 2 h and the reaction solution was concentrated under reduced pressure. The residual oil obtained was distilled to give a colorless oil, bp 67—68 °C/1.5 mmHg,††† yield 75.2%. IR (KBr): 3280 (NH), 1720 (COOEt), 1660 (C=C) cm^{-1}. NMR ($CDCl_3$): δ 8.64bs (NH), 7.07q (3-H, J=7.4 Hz), 1.82 d (4-H, J=7.5 Hz). Found: C, 43.05; H, 4.36; N, 6.11%. Calcd for $C_8H_{10}NO_3F_3$: C, 42.67; H, 4.44; N, 6.22%.

From Ethyl (Z)-2-Amino-2-butenoate and $(CF_3CO)_2O$. Into a solution of the enamine (20 mmol) and pyridine (30 mmol) in dry diethyl ether (20 ml) was added trifluoroacetic anhydride (30 mmol), with stirring, drop by drop under cooling and then the stirring was continued at room temperature for 2 h. After a further addition of ether (20 ml), the resulting solution was washed with water four times and dried ove anhydrous $MgSO_4$. After removal of ether, the residual oil obtained was distilled to give a colorless oil, yield 85.0%.

Preparation of ***10a***. Into a solution of **8a** (4.2 mmol) in dry benzene (10 ml) we stirred triethyl phosphite (4.2 mmol), drop by drop, at 0 °C. After the resulting solution had been stirred at 0 °C for 3 h, the reaction solution was concentrated under reduced pressure to give a residual syrup. The crude syrup obtained was purified on a silica-gel column using a mixture of benzene–acetone (5 : 1 v/v) as the eluent. The fraction was condensed under reduced pressure to give **10a** as a pale yellow syrup, yield 81%. IR (KBr): 3260 (NH), 1700 ($COOBu^t$), 1670 (NHCO, C=C), 1260 (>P=O), 1040 (=P–O–CH_2–) cm^{-1}. NMR ($CDCl_3$): δ 6.70 s (NH), 2.14 s ($COCH_3$), 2.06 s (γ-protons). Found: C, 50.58; H, 8.15; N, 8.16%. Calcd for $C_{14}H_{27}N_2O_5P$: C, 50.30; H, 8.08; N, 8.38%.

Preparation of ***10b***. In a similar manner, the treatment of **8b** with triethyl phosphite was worked up to give **10b** as a pale yellow syrup, yield 74%. IR (KBr): 3200 (NH), 1705 ($COOBu^t$), 1675 (NHCO, C=C), 1260 (>P=O), 1040 (=P–O–CH_2–) cm^{-1}. NMR ($CDCl_3$): δ 6.83 s (NH), 2.78 q (γ-protons, J=8.0 Hz), 2.11 s ($COCH_3$). Found: C, 51.98; H, 8.56; N, 7.91%. Calcd for $C_{15}H_{29}N_2O_5P$: C, 51.72; H, 8.33; N, 8.05%.

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†† 1 M=1 mol dm^{-3}. ††† 1 mmHg≈133.3322 Pa.