Novel Synthesis of ω-(Diphenylphosphinyl)alkylcarboxylic Acids from Triphenyl-ω-carboxyalkylphosphonium Salts

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A novel method for the synthesis of triphenylphosphonium salts of the type $(C_6H_5)_3P^+(CH_2)_nCO_2H,X^-$ (1: n = 2, 3; X = Cl; n = 5, 10, 11; X = Br) from the corresponding ω-haloalkylcarboxylic acids and triphenylphosphine has been described. When members of 1 were treated with NaH/Me_2SO/THF at room temperature under N_2, the corresponding ω-(diphenylphosphinyl)alkylcarboxylic acids 2 (n = 3, 5, 10, 11) were isolated. The yields were good (62–75%) for compounds with longer side chains (n = 10, 11). In one case (n = 3), $(C_6H_5)_3P$ was isolated as a side product (yield 20%). Attempts to prepare the Wittig reagents from 1 and the subsequent reaction with aldehydes (benzaldehyde and 9-anthraldehyde) failed to yield the expected alkenes. However, members of 2 were produced, and it was possible to recover >90% of the unreacted 9-anthraldehyde. The structures of the compounds in the series 1 and 2 have been established via the spectral properties and elemental analyses. The ^{31}P and ^{13}C chemical shifts as well as C–P coupling constants have been evaluated and analyzed. A tentative mechanism has been proposed for the formation of 2 from 1.

In the course of investigations[1] on phosphonium salts containing at least one long-chain ω-carboxylalkyl group, we have discovered that triphenyl-ω-carboxyalkylphosphonium halides 1[2] can serve as precursors in a novel conversion to ω-(diphenylphosphinyl)alkylcarboxylic acids 2. The phosphonium salts **1a–e** were easily synthesized

$(C_6H_5)_3\overset{+}{P}(CH_2)_nCO_2H,X^-$ (1)

1a, n = 2; X = Cl
b, n = 3; X = Cl
c, n = 5; X = Br
d, n = 10; X = Br
e, n = 11; X = Br

$(C_6H_5)_2\overset{O}{\overset{\uparrow}{P}}(CH_2)_nCO_2H$ (2)

via a condensation of equimolar quantities of triphenylphosphine and the corresponding ω-haloalkylcarboxylic acid 3 in toluene or xylene (2–48 h) (eq 1). Reaction conditions for the preparation of and physical properties of 1 are found in Table I.

$$X(CH_2)_nCO_2H + (C_6H_5)_3P \xrightarrow[\text{(or xylene)}]{\text{toluene, }\Delta} 1 \qquad (1)$$

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Attempted preparation of the Wittig reagents[3] of 1 using 2 equiv of solid NaH added to a solution of 1 in Me_2SO at room temperature gave the results summarized in Table II. When the solution described was treated with either benzaldehyde or 9-anthraldehyde (4),[4] there was isolated 2 along with recovered aldehyde (eq 2). Thus, the aldehyde is not involved. Both ^{31}P and ^{13}C NMR spectral data are reported in Table III for members of 1 and 2.

$$1 + 4 \xrightarrow[2.\ H_3O^+]{1.\ 2\ NaH/Me_2SO/THF} 2 \qquad (2)$$

Results and Discussion

Treatment of members of 1 with 2 equiv of sodium hydride in Me_2SO resulted in the formation of a precipitate (eq 3). Presumably, the first equivalent of NaH reacts

$$\mathbf{1b–e} \xrightarrow[Me_2SO]{NaH} \underset{\mathbf{5b–e}}{(C_6H_5)_3P^+(CH_2)_nCO_2^-} + Na^+ + X^- \qquad (3)$$

with the proton of the carbonyl group of 1 to give **5**, which is probably the solid that precipitates within about 10 min after the solution of **1** (in Me_2SO) is added (under N_2) to 2 equiv of NaH at 0 °C. The salts of **1a** and **1b** have been isolated from the reaction of aqueous NaOH on **1a** and **1b**.[2a]

When n = 10 or 11, the yields of **2c** and **2d** were 75 and 62%, respectively (Table II). With the shorter chains (n = 3 or 5), the yields were reduced, but the ease of performing the reaction argues for its utility (see Table II). Interestingly, when n = 3, triphenylphosphine was isolated (20%) as a side product. Since **1a** was reported[3] to undergo an elimination to give triphenylphosphine and acrylic acid under certain basic conditions, it was not surprising that a water-soluble mixture resulted from reaction of **1a** with NaH in Me_2SO/THF which was not analyzed further. Whether or not pentasubstituted phosphoranes are involved in this reaction cannot be defended at this time although loss of phenyl anions from such intermediates are known.[1,7] Isolation of $(C_6H_5)_3P$ (20% yield) and the low yield of **2b** indicates a completitive side reaction can also occur.

In order to test the possibility of direct solvent participation involving Me_2SO, we performed a reaction with **1d** using a $NaOC_2H_5$/DMF combination (for 24 h at room temperature). This led to **2d** (58%) and thus is strong evidence that other bases may promote the reaction and that Me_2SO is *not* a required solvent.

The spectral data summarized in Table III are in conformity with those recorded for similar systems in the literature.[8–15] Interestingly, the alternating effect observed

(1) Preliminary support from the Oklahoma State University Presidential Challenge Grant in the form of partial salary (K.D.B.) is acknowledged.

(2) Preparation of compounds **1a** (in 67% yield) and **1b** (in 42% yield) has been reported: (a) Denny, D. B.; Smith, L. C. *J. Org. Chem.* **1962**, *27*, 3404. See also: Hudson, R. F.; Chopard, P. A. *Helv. Chim. Acta* **1963**, *46*, 2178. (b) The compound **1d** has been reported to have been prepared as a glassy product (not isolated): *I. C. I. Fibres Ltd. (Belg.)* **1965**, *665*, 171; *Chem. Abstr.* **1966**, *64*, 19867b. No spectral or analytical data for **1d** were noted in the literature, however.

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(4) Certain ω-(9-anthryl)alkenylcarboxylic acids have been reported: Stoffel, W.; Michaelis, G. *Hoppe-Seyler's Z. Physiol. Chem.* **1976**, *357*, 7, 21.

(5) The compound **2a** has been reported (mp 162.5–163 °C): Mallion, K. B.; Mann, F. G. *Chem. Ind. (London)* **1963**, 654; Garner, A. Y.; Tedeschi, A. A. *J. Am. Chem. Soc.* **1962**, *84*, 4734.

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Table I. Synthetic Data for the Synthesis of Triphenyl-Substituted Phosphonium Salts of ω-Haloalkylcarboxylic Acids, $(Ph)_3P^+(CH_2)_nCO_2H,X^-$

compd (n, X)	solvent (time, h)	yield, %	mp, °C	IR,[c] cm⁻¹	¹H NMR,[a] δ	anal. calcd/obsd
1a (2, Cl)	xylene (18)	89	196-198	2840, 1730, 1430, 1380, 1320, 1110, 750, 725, 690	7.58-8.20 (br m, 15 H), 3.52 (m, 2 H), 2.86 (m, 2 H)	ref 2
1b (3, Cl)	neat[d] (2)	61	235-237	2900-2940, 1720, 1445, 1400, 1210, 760, 740, 725, 695	7.60-8.10 (br, 15 H), 3.34 (m, 2 H), 2.86 (m, 2 H), 2.19 (m, 2 H)	ref 2
1c[b] (5, Br)	toluene (24)	78	188-191	2920-2985, 1700, 1435, 1380, 1210, 1190, 1115, 745, 725, 690	9.97 (br s, 1 H), 7.74 (m, 15 H), 3.60 (m, 2 H), 2.34 (m, 2 H), 1.64 (m, 6 H)	C, 63.03/62.81; H, 5.73/5.89; P, 6.77/6.74
1d (10, Br)	toluene (30)	75	93-96	2875, 1705, 1430, 1110, 750, 720, 690	9.95 (br, 1 H), 7.74 (m, 15 H), 3.62 (m, 2 H), 2.37 (t, 2 H), 1.22-1.58 (br m, 16 H)	C, 66.03/66.12; H, 6.88/6.93; P, 5.87/5.64
1e (11, Br)	xylene (48)	65	113-115	2900, 2820, 1710, 1440, 1110, 750, 725, 690	8.76 (br, 1 H), 7.72 (m, 15 H), 3.60 (m, 2 H), 2.37 (t, 2 H), 1.20-1.60 (br m, 18 H)	C, 66.53/66.56; H, 7.07/7.13; P, 5.72/5.89

[a] All spectra were recorded in $DCCl_3$ (concentration 25-50 mg/0.5 mL in a 5-mm tube) except for 1a and 1b ($DCCl_3$ + 10% trifluoroacetic acid), and chemical shifts are from Me_4Si as internal standard. The spectrum for 1a in Me_2SO-d_6 showed the following signals: δ 7.82 (m, 16 H, 15 ArH and 1 CO_2H), 3.0 (m, 2 H), 2.76 (m, 2 H). [b] See ref 2b. [c] KBr pellet. [d] At 180 °C.

Table II. Synthetic Data for the Formation of ω-(Diphenylphosphinyl)alkylcarboxylic Acids, $(Ph)_2P(O)(CH_2)_nCO_2H$

compd (n)	yield, %	mp, °C	IR,[c] cm⁻¹	¹H NMR,[a] δ	anal. calcd/obsd
2b (3)	17	155-156	2840-2890, 1710, 1440, 1220, 1150-1170, 1125, 780, 745, 730, 695	7.2-8.1 (m, 11 H, including 10 ArH and 1 COOH), 2.44 (m, 4 H), 1.94 (m, 2 H)	C,[b] 66.66/66.87; H, 5.94/6.00; P, 10.74/10.92
2c (5)	32	136-137	2830-2925, 1730, 1440, 1260, 1150-1170, 725	8.13 (br s, 1 H), 7.40-7.84 (m, 10 H), 2.29 (m, 4 H), 1.20-1.90 (m, 6 H)	C, 68.35/68.16; H, 6.69/6.84; P, 9.79/10.01
2d (10)	75	62-62.5	2890, 2820, 1715, 1435, 1250, 1190, 1145, 1135, 1100, 720-745, 700, 690	11.08 (br s, 1 H), 7.38-7.84 (m, 10 H), 2.31 (m, 4 H), 0.90-1.90 (m, 16 H)	C, 71.48/71.79; H, 8.08/8.54; P, 8.01/8.16
2e (11)	62	119-120	2890, 2825, 1715, 1440, 1250, 1160, 1120, 1100, 720-730, 700, 690	11.86 (br s, 1 H), 7.38-7.86 (m, 10 H), 2.30 (m, 4 H), 1.02-1.90 (m, 18 H)	C, 71.98/71.81; H, 8.31/8.38; P, 7.73/7.64

[a] All spectra were recorded in $DCCl_3$ (concentrations of 25-50 mg/0.5 mL in a 5-mm tube), and chemical shifts are from Me_4Si as internal standard. The downfield signal for the acid proton in **2a** was found buried under the aromatic signals. [b] Reference 5 contains the preparation of **2b**, but no elemental analysis was included. [c] KBr pellet.

on both the chemical shifts and the coupling constants for the aromatic carbon atoms in both the systems **1a–e** and **2b–e** probably indicates that some kind of electronic effect is operative in the bonds (for example, pπ–dπ-type overlap).[16] The alternating effect on the chemical shifts of the side-chain carbons (and the coupling constants involved) is also experienced by α, β and γ carbon atoms in the above systems.[14]

Experimental Section

General Methods. The melting points reported are uncorrected. NMR spectra were obtained on a Varian XL-100(15) NMR spectrometer equipped with a Nicolet TT-100 PFT accessory operating at 100.1 MHz for ^1H, at 40.5 MHz for ^{31}P, and at 25.1 MHz for ^{13}C. Concentrations of solutions varied from 100–200 mg/2 mL in a 12-mm tube for ^{13}C and ^{31}P spectra and in a 5-mm tube for ^1H spectra. For ^{13}C spectral analysis, a pulse width of 10–14 s (45°) was used to aid in the acquisition of the slower relaxing carbons. Total delay time between pulses was a summation of the acquisition time (1.36 s) and an additional delay time of 6–8 s. For ^{31}P spectra, a pulse width of 9–11.8 μs (45°) was used. Acquisition time was 1.36 s, and the additional delay time was 6–20 s. The total number of acquisitions for obtaining ^{13}C and ^{31}P spectra varied between 400 and 9100 for ^{13}C and between 16 and 340 for ^{31}P spectra, respectively. Infrared spectral data were obtained on a Beckman IR-5A unit. All solvents were dried and freshly distilled and stored according to standard procedures.[17] Elemental analyses were performed by Galbraith Laboratories.

Preparation of 1a. A mixture of 5 g (0.019 mol) of triphenylphosphine (J. T. Baker Co., mp 79–81 °C) and 2.5 g (0.023 mol) of β-chloropropionic acid [Aldrich, freshly distilled, bp 203–205 °C (760 mm)] was dissolved in 50 mL of dry xylene. The mixture was boiled under N_2 (with magnetic stirring) for a period of 18 h. The mixture turned cloudy in 20 min, and, in the course of 18 h, an oil had separated. As the mixture cooled, the oil solidified. The solid was washed with ether and dissolved in 100 mL of CH_2Cl_2. The solution was filtered, and 1a was precipitated with ether: white solid; mp 196–198 °C; 6.25 g (89%). For spectral data, see Tables I and III.

Preparation of 1b. Heating a mixture of 3.0 g (0.0115 mol) of triphenylphosphine and 1.4 g (0.0115 mol) of $Cl(CH_2)_3CO_2H$ [Aldrich, bp 85–88 °C (0.75 mm)] without solvent under N_2 in an oil bath at 180 °C for 2 h (followed by cooling) produced a transparent solid. A minimum quantity of acetone was added

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Table III. ^{31}P and ^{13}C Chemical Shifts and ^{13}C–^{31}P Coupling Constants in Systems[a,b] 1a–e and 2b–e

	chemical shifts, ppm (J_{CP}, Hz)									
	phosphonium salts					phosphine oxides				
atom	1a (n = 2)	1b (n = 3)	1c (n = 5)	1d (n = 10)	1e (n = 11)	2b (n = 3)	2c (n = 5)	2d (n = 10)	2e (n = 11)
^{31}P[c]	24.5	23.5	24.0	24.0	23.9	35.0	34.8	34.4	34.6
C(1)	117.9 (86.1)	118.1 (85.4)	117.9 (86.0)	118.0 (86.0)	117.9 (86.0)	131.6 (99.5)	132.0 (99.3)	132.2 (98.6)	132.4 (98.6)
C(2,6)	133.4 (10.1)	133.5 (10.2)	133.4 (9.7)	133.3 (9.7)	133.3 (10.2)	130.7 (9.6)	130.6 (9.5)	130.6 (9.0)	131.0 (9.5)
C(3,5)	130.0 (11.1)	130.0 (12.5)	130.4 (12.4)	130.4 (12.5)	130.3 (12.5)	128.6 (12.2)	128.5 (11.7)	128.5 (11.8)	128.8 (11.8)
C(4)	134.7[d]	134.6[d]	135.0 (2.4)	135.0 (2.9)	135.0 (2.4)	131.8 (2.8)	131.7 (2.0)	131.6 (2.3)	132.0 (2.8)
C(1′)	170.8 (17.0)	172.8	175.6	176.5	176.6	174.9	176.3	176.9	176.9
C(2′)			34.2	34.5	34.4		33.8	34.3	34.7
C(3′)			24.0	24.7	24.7		24.3	24.9	25.3
$(CH_2)_m$[e]				28.8–29.0	28.9–29.0			28.9–29.1	29.3–29.6
C(γ)		33.6 (17.9)	29.5 (16.1)	30.2 (15.5)	29.8 (15.7)	34.5 (13.9)	30.2 (16.1)	30.7 (14.7)	31.1 (14.7)
C(β)	26.9 (2.7)	17.7 (2.3)	22.0 (4.4)	22.4 (4.4)	22.4 (4.0)	17.4 (3.7)	21.0 (3.3)	21.2 (3.6)	21.6 (3.8)
C(α)	17.9 (54.9)	19.8 (49.5)	22.5 (51.4)	22.6 (50.4)	22.5 (50.1)	28.5 (71.4)	29.1 (71.2)	29.4 (72.2)	29.7 (71.5)

[a] Numbering system is as follows:

[b] All spectra were recorded in $DCCl_3$ except for 1a (in Me_2SO-d_6) in the PFT mode. ^{31}P and ^{13}C chemical shifts are from 85% H_3PO_4 as external standard and Me_4Si as internal standard, respectively. Positive chemical shifts are downfield from the standard (resolution 0.3 Hz). The numbers in parentheses indicate the C–P coupling constants. [c] The ^{31}P spectrum was obtained from a solution of 1a in a mixture of Me_2SO-d_6 and $DCCl_3$ (1:1) (50 mg/2 mL)). [d] The signals were broad due to unresolved coupling. [e] The signals were too close for individual assignments to be made for C(4′)–C(8′) in 1d and 2d and for C(4′)–C(9′) in 1e and 2e.

to dissolve the solid which was precipitated with ether. After the solid was washed with ether and dried in vacuo for 2 h, a white powder was obtained: mp 235–237 °C; 2.7 g (61%) of **1b**. For spectral data see Tables I and III. In a second experiment, starting from 3.82 g (0.015 mol) of triphenylphosphine and heating without solvent under N_2 on an oil bath at 135–140 °C for a period of 20 h followed by cooling and washing with ether, there was obtained 2.9 g (52%) of **1b**, mp 231–234 °C. When toluene or xylene was used as a solvent, the yield of **1b** was less than 5%. In another experiment 13.1 g (0.05 mol) of triphenylphosphine and 6.1 g (0.05 mol) of $Cl(CH_2)_3CO_2H$ were heated together without solvent under N_2 in an oil bath at 140–145 °C for a period of 24 h. A solid formed which was washed with 100 mL of ether and recrystallized from CH_3OH–ether. The white solid, which separated first from CH_3OH–ether upon standing overnight, redissolved, and an oil was obtained. After the solvent was stripped off in a rotary evaporator and the residue triturated with dry ether, a white solid formed: 15.9 g; mp 136–139 °C. This material proved to be a mixture of 90% of the methyl ester of **1b** and 10% of **1b** as determined by spectral analysis and a neutralization equivalent determination.

Preparation of 1c. The salt **1c** was prepared by heating together 5.24 g (0.020 mol) of triphenylphosphine and 3.9 g (0.020 mol) of $Br(CH_2)_5CO_2H$ [Aldrich, freshly distilled, bp 152–154 °C (18 mm)] in 75 mL of dry toluene at reflux under N_2 for a period of 24 h. After the flask was cooled, an oil separated. The solvent was removed in a rotary evaporator and a glasslike, heavy oil separated. This oil was triturated with dry ether which resulted in the formation of a white solid. After recrystallization from $HCCl_3$–ether (1:10) (and washing with 100 mL of ether), a solid formed and melted at 188–191 °C [yield 7.1 g (78%)]. For analytical and spectral data of 1c, see Tables I and III.

Preparation of 1d. The procedure was exactly as reported above for the preparation of **1c**. From 5.3 g (0.020 mol) of triphenylphosphine and 4.72 g (0.018 mol) of $Br(CH_2)_{10}CO_2H$ (Aldrich, mp 48–51 °C) was obtained 7.5 g (75%) of **1d** (mp 93–96 °C). For analytical and spectral data see Tables I and III.

Preparation of 1e. The procedure was exactly as reported above for the preparation of **1c** except for the use of xylene in place of toluene. Also the reaction time was lengthened to 48 h. From 2.62 g (0.010 mol) of triphenylphosphine and 2.9 g (0.010 mol) of $Br(CH_2)_{11}CO_2H$ (Aldrich, 97% mp 52–55 °C) was obtained 3.5 g (65%) of **1e** (mp 113–115 °C). For analytical and spectral data see Tables I and III.

Preparation of 2b. A solution of 1.5 g (0.0039 mol) of **1b** in 25 mL of freshly distilled, dry Me_2SO[17] was added to dry NaH (Alfa, 99%) under N_2 (cooling in ice) over a period of 10 min. A colorless solid precipitated (**5b**?) in about 10 min with evolution of a colorless gas (H_2). After the addition of **1b** was completed, the solid was dissolved gradually by addition of ca. 20 mL of dry THF, and the mixture was allowed to rise to room temperature by removing the ice bath. The reaction mixture was stirred at room temperature under N_2 for a period of 4 days. The reaction was quenched by pouring the mixture into ca. 150 mL of distilled water. The resulting solution was acidified with 6 N HCl to pH ~1.0. Extracting the mixture with 200 mL of ether (three times), washing the ether layer with distilled water, drying (Na_2SO_4) the ether layer, and stripping off the ether on a rotary evaporator produced a yellow oil. After addition of dry hexane and refrigeration, the solution yielded a solid. The solid was washed with dry hexane (100 mL). Recrystallization from $HCCl_3$–hexane (1:10) afforded a colorless solid, **2b**: mp 155–156 °C; 150 mg (13%). For spectral data see Tables II and III. The washings from hexane yielded 200 mg (19%) of solid (mp 79–80 °C) identified as $(C_6H_5)_3P$ from a mixture melting point determination (79–80 °C) with an authentic sample. In addition, the IR and ^1H NMR spectra were identical with that of an authentic sample of $(C_6H_5)_3P$.

Preparation of 2c. A solution containing 1.37 g (0.003 mol) of **1c** in 20 mL of dry Me_2SO was added to 177 mg (0.074 mol) of dry NaH under N_2 at 0 °C over a period of 5 min. A solid (**3c**?) separated with the evolution of gas (H_2). The solid was dissolved by adding 20 mL of dry THF and raising the temperature to room temperature gradually. The reaction mixture was stirred under N_2 at room temperature for a period of 36 h, at which time the solution became light yellow. A solution of 0.665 g (0.003 mol)

of 9-anthraldehyde (Aldrich, mp 103–105 °C) dissolved in 20 mL of THF was added to the reaction mixture over a period of 30 min, and stirring under N_2 was continued at room temperature for an additional 4 days. During this period (the flask was protected from light) a yellow solid precipitated out. The reaction mixture was poured into 200 mL of ice-cold water. The mixture was acidified with 6 N HCl to pH ~1.0. The product was extracted seven times with ether (total quantity of 100 mL). The ether layer (A) was extracted with 100 mL of 10% NaOH (three times) and washed twice with distilled water. Acidification of the basic extract with 6 N HCl gave a yellow solid. The solid was reextracted with 100 mL of ether (three times), and the solvent was evaporated in a rotary evaporator. This solid **2c** was recrystallized ($HCCl_3$): mp 136–137 °C; 300 mg (32%). For analytical and spectral data, see Tables II and III. From the neutral ether layer (A), 600 mg (97%) of 9-anthaldehyde was recovered.

Preparation of 2d. The procedure was exactly like that used for the preparation of **2c**. From 0.108 g (0.004 mol) of NaH, 1.06 g (0.002 mol) of **1d**, and 0.443 g (0.002 mol) of 9-anthraldehyde (4) after a reaction period of 6 days at room temperature there was obtained 0.580 g (75%) of pure **2c** (recrystallized from ether–petroleum ether), mp 62–62.5 °C. It was possible to recover 9-anthraldehyde (87%) as described earlier.

In another experiment and in the absence of anthraldehyde, 0.108 g (0.004 mol) of NaH and 1.06 g (0.002 mol) of **1d** afforded 0.550 g (71%) of **2d**.

Reaction of 1d with $NaOC_2H_5$ and DMF. In an effort to assess the possible role of a direct participation of Me_2SO in the reaction, the combination of $NaOC_2H_5$/DMF was used instead of NaH/Me_2SO. With 1.06 g (0.002 mol) of **1d** and 0.265 g (0.004 mol) of freshly prepared $NaOC_2H_5$ in 20 mL of DMF and a reaction time of 24 h at room temperature, it was possible to isolate 0.450 g (58%) of **2d**.

Attempted Preparation of the Wittig Reagent of 1d and Reaction with Benzaldehyde. An experiment was also performed with benzaldehyde instead of 9-anthraldehyde (4) using NaH/Me_2SO/THF. With 0.153 g (0.0064 mol) of NaH, 1.59 g (0.003 mol) of **1d**, and 0.32 g (0.003 mol) of freshly distilled benzaldehyde (with 40 mL of Me_2SO and 40 mL of THF) and after a reaction period of 5 days at room temperature (under N_2), 0.500 g (43%) of **2d** was isolated by following the workup procedure described in the preparation of **2d**. Proton NMR analysis of the neutral, ether-soluble portion revealed a large quantity of benzaldehyde.

Preparation of 2e. The oxide **2e** was prepared by a procedure similar to the one described for the preparation of **1d**. From 0.198 g (0.0082 mol) of dry NaH and 2.17 g (0.004 mol) of **1e** (with 30 mL of Me_2SO and 10 mL of THF) and with a reaction time of 4 days at room temperature (under N_2) there was formed a white solid (recrystallized from $HCCl_3$–hexane): mp 120–121 °C; 1.0 g (62%) of **2e**. For analytical and spectral data, see Tables II and III.

Registry No. 1a, 36626-29-6; **1b**, 60633-18-3; **1b** methyl ester, 73367-74-5; **1c**, 50889-29-7; **1d**, 7530-96-3; **1e**, 73367-75-6; **2b**, 73367-76-7; **2c**, 73367-77-8; **2d**, 73367-78-9; **2e**, 73367-79-0; **3a**, 107-94-8; **3b**, 627-00-9; **3c**, 4224-70-8; **3d**, 2834-05-1; **3e**, 73367-80-3; **4**, 642-31-9; **5b**, 73367-81-4; triphenylphosphine, 603-35-0; benzaldehyde, 100-52-7.

Synthesis of Benzothiazoles. α-Amino-(4-hydroxy-6-benzothiazolyl)propionic Acid

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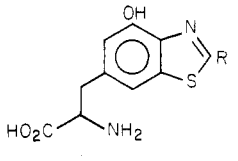
The tentative structure assigned to the photobiologically important skin pigment pheomelanin is based on degradative studies of the natural chromophore. The title compound was reported to be one of several key amino acids isolated in these studies. The identity of this benzothiazole derivative has now been confirmed via an unambiguous eight-step total synthesis starting from 5-methyl-2-nitrophenol.

We have demonstrated that pheomelanin, the red-brown polymeric pigment found in the skin and hair of fair-skinned humans,[2] is photolabile under physiologically relevant conditions.[3,4] This pigment is composed of a chromophore covalently bonded to a protein fraction. Since the protein is neither involved in nor altered during photolysis,[4b,5] we focused our attentions on the photochemistry of the chromophore. Unfortunately, due to problems with homogeneity and solubility, the chromophore has yet to be properly characterized. However, degradation of the protein-free chromophore by hot concentrated hydriodic acid afforded amino acids **1** and **2** as major products. Isolated as their methyl esters and assigned structures based on spectroscopic data, these two



1, R = H
2, R = CH_3

amino acids, along with degradation products isolated from permanganate oxidation of the chromophore served as the basis for the conclusion that the dominant monomeric unit in the chromophore is a benzothiazole moiety.[2] We report herein a synthesis of amino acid **1** which confirms the identity of one of the amino acids isolated in the aforementioned degradative studies.

At the outset, two synthetic approaches were considered as follows: (1) start with the benzothiazole ring system and build onto it the appropriate functionality, or (2) form the thiazole ring by annelation of a suitably substituted aniline. Benzothiazoles are reported to undergo electrophilic aromatic substitution to give 6-substituted benzothiazoles as the major product,[6] and a second electrophilic substitution

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