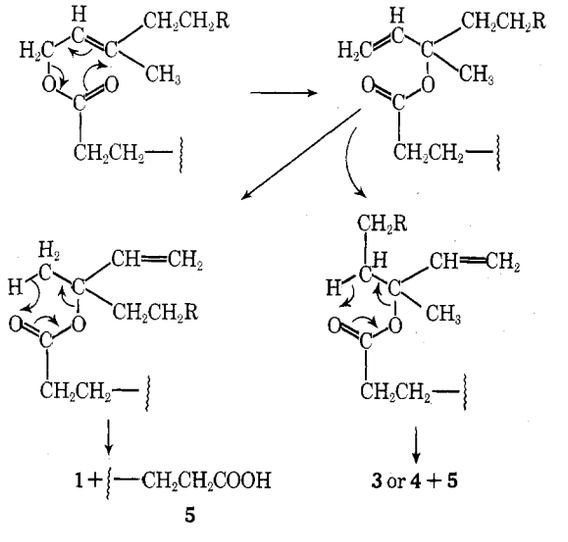
Scheme I



R = $(CH_3)_2CHCH_2CH_2CH_2CH(CH_3)CH_2CH_2CH_2CH(CH_3)CH_2$—

strated by isolation of 4-acetoxy-*trans*-2-heptene in the pyrolysate.[3]

It should be noted that tobacco smoke contains several phytadiene isomers, the most abundant of which is neophytadiene.[4] Since all of the phytadienes reported in Table I (except **2**) have been found in tobacco smoke, it seems likely that pyrolysis of the residual phytol esters originally present in tobacco as chlorophyll produces some of the phytadienes observed in smoke.

Besides tobacco, the only other reported occurrence of phytadienes is in zooplankton.[2] Since an injector port temperature of 250° is sufficient to produce phytadienes from pheophytin a, before reporting the presence of phytadienes in an extract it is important to demonstrate the absence of chlorophyll or its degradation products in that extract. In this respect it is possible that the phytadienes reported to be present in zooplankton[2] may have been an artifact.

Experimental Section

The samples were pyrolyzed directly into the gas chromatographic column using a CDS Pyroprobe 190 system. The sample (*ca.* 300 μg) was coated from solution (CH_2Cl_2) on a platinum ribbon (35 × 1.5 × 0.0127 mm); after solvent evaporation, the ribbon assembly was inserted into the injection port of the chromatograph (held at 240 ± 10°). After restabilization of the helium carrier gas flow (1–2 min), the ribbon was heated at 10°/msec to 250, 350, or 400° and held there for 2 sec. Pyrolysis products were immediately vaporized and swept onto the gc column. The estimated maximum residence time of the products at temperature was less than 100 msec; thus isomerization was avoided.

Samples were also pyrolyzed by injecting the solution (CH_2Cl_2) directly into the heated injection port. Injector temperatures of 250–320° were sufficient to pyrolyze the pheophytin a to give a low yield (5–10%) of phytadienes. Although the results of injector port pyrolyses were not as reproducible as those of the platinum ribbon system, the identities and distribution of products were approximately the same as shown in Table I.

Two gc columns were used: (a) 300 ft × 0.01 in. i.d. stainless steel, wall coated with SF-96 containing 5% Igepal 880 operated isothermally at 180° (110,000 theoretical plates), and (b) 150 ft × 0.02 in i.d. stainless steel, wall coated with OV-101; temperature programmed from 130 to 200° at 3°/min. Both columns gave identical retention indexes and the resolution was such as to verify that there were no more than four phytadienes present. The computerized combined gas chromatograph–mass spectrometer system has been described previously;[5] however, since capillary columns with carrier gas flow rates of 0.5–1.5 ml/min were used for this study and since the restrictors in the fritted glass interface between the gas chromatograph and mass spectrometer were adjusted for flow rates of 15–40 ml/min, it was necessary to add carrier gas after the column to bring the total gas flow into the interface up to these higher values. A flame ionization detector chromatogram was recorded in parallel to the gas chromatograph–mass spectrometer and was used for the quantitative values shown in Table I.

Pheophytin a was prepared by acid hydrolysis[6] of chlorophyll a which was, in turn, isolated from a mixed culture of green algae and blue-green algae (cultured in a modified Allen's medium[7] for 3 weeks). The cells were collected by centrifugation, and the chlorophyll a was isolated by chromatographic procedures.[6] The visible spectrum of the isolated pheophytin a (in ether) exhibited peaks at 410, 474, 506, 535, 562, 612, and 671 nm and was in agreement with published spectra.[8] Methyl pheophorbide a was prepared by Fisher's method,[6] and the mass spectrum was obtained by inserting the sample directly into the ion source at 380°; it showed characteristic ions at *m/e* 606, 576, 548, and 461 and agreed with the published mass spectrum of methyl pheophorbide a.[9]

Acknowledgments. Iwan Hirsan provided valuable assistance; the instrumentation was supported (in part) by National Institutes of Health Research Grant RR00317 from the Division of Research Facilities and Resources (K. Biemann, principal investigator).

Registry No.—1, 504-96-1; **2**, 51806-25-8; **3**, 21980-71-2; pheophytin a, 603-17-8.

Supplementary Material Available. Complete mass spectra of compounds **1–4** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2634.

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A New, Practical Synthesis of L-2-Hydroxytryptophan and Its Derivatives

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DL-2-Hydroxytryptophan[2] (**3**) has been prepared by three- or four-step syntheses originating with the reaction products from ethyl 2-(*o*-nitrophenyl)acetate and diethyl methylenemalonate,[3] isatin and ethyl pyruvate,[4] or 3-chloromethyleneoxindole and diethyl formamidomalonate.[5] Yields, however, are modest (15–24% overall) and resolution, when the biologically important[3-6,8,9] L isomer is desired, poses difficulties.[4]

A one-step oxidation of L-tryptophan with peracetic acid in acetic anhydride[6,7] or aqueous hydrolysis (130°) of its symmetrical 2,2′-disulfide,[8] obtained by reaction with di-

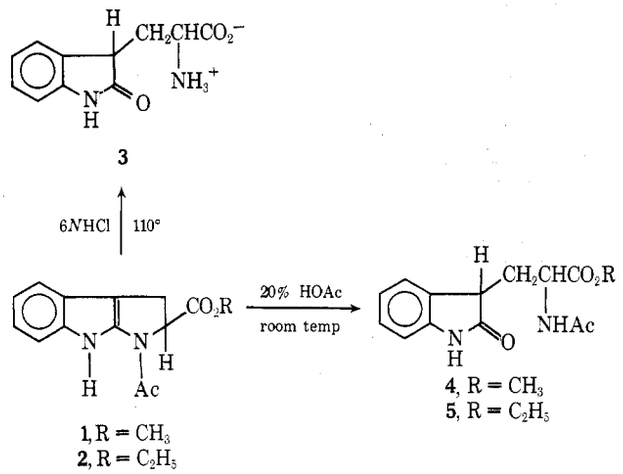
sulfur dichloride, affords the L isomer directly, although yields are still low.

A recent modification of the latter reaction, whereby 2-thio(4-nitrophenyl)-L-tryptophan is hydrolyzed with 20% aqueous acetic acid at 110°, is reported to give **3** in 70% yield.[10] The starting material is easily prepared by reaction of L-tryptophan with 4-nitrophenylsulfenyl chloride in acetic acid. This procedure and most likely the disulfide hydrolysis above suffer a limitation in being applicable only to tryptophan or tryptamine derivatives having a free amino group which apparently participates in the hydrolysis.[10]

We wish to report a convenient, high-yield procedure for the synthesis of L-2-hydroxytryptophan, which is also suitable for the preparation of *N*-acyl, ester derivatives.

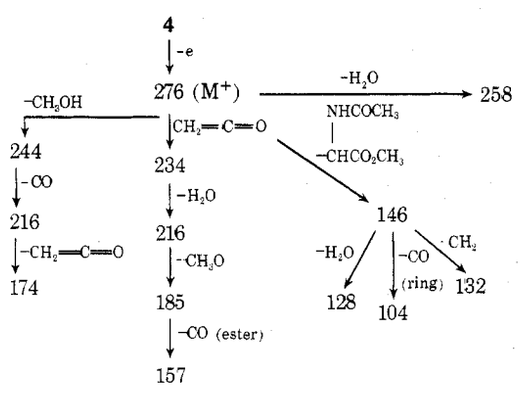
The method consists in the acidic hydrolysis of 2,3-dihydropyrrolo[2,3-*b*]indoles (*e.g.*, **1** and **2**) which are synthesized easily in a one-step oxidation of *N*-acetyl-L-tryptophan methyl or ethyl ester with *N*-bromosuccinimide at pH 8.5–9.0 or preferably with *tert*-butyl hypochlorite in triethylamine-buffered methylene chloride.[11] Sealed-tube hydrolyses (110°) of either **1** or **2** with constant-boiling HCl afforded **3** in 75% yield after conversion to the free amino acid by a Dowex-1 (acetate form) column in order to remove HCl (**3** is unstable toward alkali[5]), while hydrolysis with 20% acetic acid at room temperature provided the *N*-acetyl methyl (**4**) and ethyl (**5**) esters of **3** in 63 and 74% yields, respectively. When the room-temperature hydrolysis was performed with 0.1 *N* HCl, side reactions intervened and the yields of **4** or **5** decreased (Scheme I).

Scheme I



A low-resolution mass spectrum of **4** is consistent with the fragmentation pathways as indicated in Scheme II. The base peak at *m/e* 146 probably corresponds to the 3-methyleneindolin-2-one ion. This ion apparently loses methylene, H_2O, or CO to give ions at *m/e* 132, 128, and 104, respectively. A mass spectrum of **5** indicated fragmentations analogous to those of **4** and exhibited metastable peaks at *m/e* ~255 and ~112 (among others) corresponding to the loss of H_2O from the parent ion (*m/e* 290) and base peak (*m/e* 146), respectively.

Scheme II



A 100-MHz pmr spectrum of **3** in D_2O containing sufficient DCl for dissolution reveals an unexpectedly complex pattern which is interpreted as originating from a 1:1 mixture of 3*S*,α*S* and 3*R*,α*S* diastereoisomers. In addition to a common aromatic multiplet at δ 7.10–7.60 (relative to the internal HOD reference at δ 5.00), the following signals are observed. One isomer gives rise to a one-proton triplet (J = 6.5 Hz) at δ 4.60 coupled to a two-proton AB-type quartet (δ_A 2.66, δ_B 2.53; J_{AB} = 15 Hz; eight lines) with signals assigned to the α proton and β-methylene protons, respectively. The α-proton triplet of the other isomer (no attempt is made to assign stereochemistry) is centered at δ 4.48 (J = 7.0 Hz) and likewise splits the β-methylene AB quartet (δ_A 2.81, δ_B 2.45; J_{AB} = 15 Hz) into eight lines. The two NH protons and the 3-H proton are exchanged under these conditions. The pmr spectrum of **4** (see Experimental Section) reveals a much simpler spectrum in which diastereoisomers cannot be distinguished.

Experimental Section

Melting points are uncorrected. Thin layer chromatography was performed in ethyl acetate–methanol (9:1 v/v) (solvent 1) or 1-butanol–acetic acid–water (4:1:5 v/v, upper layer) (solvent 2). Spots were detected by ninhydrin or 47% HBr followed by heating. Ultraviolet spectra were measured on a Shimazu UV-200 spectrophotometer equipped with a U-125 MU recorder. Infrared spectra were obtained with a Hitachi Perkin-Elmer Model 225. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Pmr spectra were obtained on a Varian Associates HA-100 spectrometer. Chemical shifts are reported as δ values (parts per million) with tetramethylsilane or HOD as an internal reference. Low-resolution mass spectra were measured with a double-focusing Hitachi RMU-6E spectrometer.

L-2-Hydroxytryptophan [L-3-(2-Amino-2-carboxyethyl)indolinone, 3]. The pyrroloindole **2**[11] (1.25 g, 4.5 mmol) was dissolved in constant-boiling hydrochloric acid (40 ml) and heated at 110° for 20 hr in a sealed tube. The dark yellow solution was evaporated nearly to dryness. The residue was dissolved in water, decolorized with charcoal, and dried by evaporation. It exhibited a single band on high-voltage paper electrophoresis (pH 2.08). The hygroscopic syrup was dissolved in water (25 ml) and passed through a 1.8 × 10 cm column of Dowex-1 (acetate form, 100–200 mesh) and the column was washed with water. The eluate was filtered through Toyo filter paper No. 5c and lyophilized to give 0.75 g (75%) of material, mp 233–235°, which proved to be 98.5–99% pure by amino acid analysis in pH 5.82 buffer on a short column where its peak just preceded that of tryptophan. This product (200 mg) was dissolved in oxygen-free water (0.6 ml) and the solution was stirred gently with a spatula. Crystals appeared spontaneously. Crystallization was complete after several hours in the refrigerator. The crystals were separated by centrifugation and dried *in vacuo* over P_2O_5: 130 mg; mp 248–250°; $[\alpha]^{20}D$ +39.8° (*c* 2.13, 1 *N* NaOH) [lit. mp 244–245° dec,[4] 246–247° dec,[8] 248–249° dec,[3] 249–253° dec,[9] 250–252°,[10] 254–256°,[6] 256° dec;[5] +21°,[6] +20.6°,[8] +30.1°,[10] +31.8°,[8] +39.2°[9] (*c* 0.81–2.75, 1 *N* NaOH)]; R_f 0.60 (2); λ_{max} (H_2O) 250 nm (ε 6900), shoulder 280 (1400) [lit. λ_{max} (H_2O) 250 nm[10,12] (ε 7200),[10] 7250)[12]]; λ_{max} (KBr) 3300–2600 (broad), 1625, 1565, 1470, 1390, 1325 cm^{-1}; pmr, see text.

Attempted crystallization from aqueous ethanol produced sizable amounts of ninhydrin-positive impurities and led to a poor recovery.

Anal. Calcd for $C_{11}H_{12}O_3N_2$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.78; H, 5.54; N, 12.85.

L-3-(2-Acetamido-2-methoxycarbonylethyl)indolinone (4). The pyrroloindole **1**[11] (490 mg, 1.90 mmol) was dissolved in 20% acetic acid (45 ml) with stirring. The reddish solution which resulted within 10 min was stirred for 50 min and lyophilized. The pale yellow residue was chromatographed over silica gel (contain-

ing 12% alumina, 325 mesh and finer, product from Nakarai Chemicals Inc., Kyoto) and eluted with ethyl acetate–methanol (9:1 v/v). Homogeneous fractions (checked by tlc) were combined and evaporated below 35° nearly to dryness. Crystallization resulted on standing under petroleum ether in a refrigerator. The crystals were crushed and filtered to give 330 mg (63%) of an almost colorless product: mp 148–150°; $[\alpha]^{20}D$ −16.5° (c 2.38, $CHCl_3$); R_f 0.83 (1); λ_{max} (EtOH) 250 nm (ε 7000), shoulder 280 (1470); ν_{max} ($CHCl_3$) 3435, 3300–3200 (broad), 3000, 1730, 1720, 1670, 1620, 1470, 1440, 1370, 1330 cm^{-1}; pmr (100 MHz, $CDCl_3$) δ 9.18 (broad, one proton, NH of oxindole, exchanges rapidly with D_2O), 6.86–7.52 (five protons, aromatic multiplet + NHAc, exchanges slowly over several hours with D_2O), 4.98 [one-proton quartet, $J \simeq 7$ Hz, α proton, changes slowly to two overlapping doublets, 4.95 (J = 6 Hz) and 4.87 (J = 7 Hz), on D_2O exchange], 3.70 (three-proton singlet, OCH_3), 3.50 (one-proton triplet, J = 6 Hz, 3-H), 2.38 (two-proton skewed triplet, $J \simeq 7$ Hz, collapses to doublet, J = 7 Hz, on irradiation at center of 4.96 triplet, β-CH_2 groups), 2.02 ppm (three-proton singlet, NAc) The fragmentation on low-resolution mass spectrometry is shown in Scheme II.

Anal. Calcd for $C_{14}H_{16}O_4N_2$: C, 60.86; H, 5.84; N, 10.14. Found: C, 61.12; H, 5.86; N, 10.05.

L-3-(2-Acetamido-2-ethoxycarbonylethyl)indolinone (5). The pyrroloindole 2[11] (400 mg, 1.47 mmol) was dissolved in 20% acetic acid (40 ml) with stirring. The solution was treated in the same manner as the methyl ester analog above. The crude product (150 mg) was chromatographed on silica gel and eluted with ethyl acetate–methanol (9:1 v/v). Homogeneous fractions were pooled and evaporated. The syrupy residue failed to crystallize and was stored under vacuum, then pulverized. The resulting amorphous powder was collected with petroleum ether to afford 112 mg: mp 113–117°; R_f 0.85 (1); λ_{max} (EtOH) 250 nm (ε 6800), shoulder 280 (1420); ν_{max} ($CHCl_3$) 3420, 3300–3200, 2950, 1720, 1670, 1620, 1470, 1440, 1370 cm^{-1}; M^+ m/e 290. The fragmentation pathways were similar to those of **4**.

Anal. Calcd for $C_{14}H_{18}O_4N_2$: C, 62.05; H, 6.25; N, 9.65. Found: C, 62.27; H, 6.51; N, 9.54.

Registry No.—**1**, 25690-48-6; **2**, 21018-88-2; **3**, 32999-55-6; **4**, 51806-22-5; **5**, 40846-93-3.

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New Syntheses in Dihydrojasmone Series

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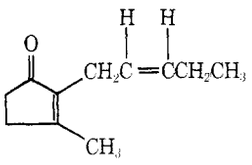
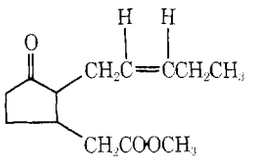
cis-Jasmone and methyl jasmonate are primary odorous principles of the flower oils of several varieties of *Jasminum*. Several syntheses of jasmone[1-5] and methyl jasmonates[6-8] have been published. Dihydrojasmone (**6**) is closely related to jasmone both in structure and in odor, is useful in perfumery, and has been synthesized by several procedures.[5,9-12]


cis-jasmone


methyl jasmonate

We wish now to describe an efficient five-step synthesis of dihydrojasmone (**6**) and tetrahydrojasmone (**7**), and a seven-step synthesis of methyl dihydrojasmonate (**12**). The starting point in the present synthetic scheme was the alkylation of 2-carbethoxycyclopentanone(**1**). This was accomplished by using NaH in DMF with RBr.[13] The key intermediate **3** was prepared by acid hydrolysis of **2**.[14] 2-Pentylcyclopentan-1-one (**3**) was then treated with isopropenyl acetate, yielding **4**, which was converted into **5** by the bromination–dehydrobromination method.[15] Methylation of **5** with methyllithium and oxidation of the resulting carbinol with chromium trioxide[8,16] led to the expected dihydrojasmone (**6**). The cuprous chloride catalyzed addition of a Grignard reagent, CH_3MgI, to **5** formed tetrahydrojasmone (**7**). Michael addition of dimethyl malonate to **5** yielded **8**, which upon hydrolysis and decarboxylation[8,17] was transformed to dihydrojasmonic acid (**9**), which was methylated to yield methyl dihydrojasmonate (**12**). We also explored a different route for synthesis of **12**, *via* intermediates **10** and **11**. Methyl-2-pentylcyclopent-2-en-1-ol acetate (**10**) was prepared either by treating **5** with lithium methyl acetate or with Reformatzky reagent.[18]

The lithium method seemed more elegant and attractive; it yielded 82% of **10**, as compared to 60% by Reformatzky's method. Oxidation of **10** with chromium trioxide afforded **11**, which was reduced catalytically to **12**.[17] Methyl dihydrojasmonate (**12**) prepared by both methods had identical spectroscopic (ir, nmr), and chromatographic properties.

It is noteworthy that compounds **6**, **11**, and **12** possess the characteristic long-lasting jasmone-like odors. The advantages of the present synthesis is that the starting materials are relatively inexpensive and easily accessible and the overall yields of the products are satisfactory.

Experimental Section

Microanalyses were performed at the Microanalytical Laboratory of the Hebrew University. Melting points were determined on a Thomas-Hoover apparatus. The following spectrometers were used: nuclear magnetic resonance (nmr), Varian T-60; infrared (ir), Perkin-Elmer Model 137; mass spectrometer (mass spectrum), Varian MAT-311; ultraviolet (uv), Unicam SP-800; vapor phase chromatography (vpc) analyses were performed on a Varian Aerograph 90-P instrument using a 3% SE-30 column. Infrared spectra were measured in sandwich cells (sc), uv spectra in ethanol, and nmr spectra in deuteriochloroform, unless otherwise stated.

2-Pentyl-2-carbethoxycyclopentan-1-one (2). 2-Carbethoxycyclopentanone(308 g, 1.97 mol) was added dropwise under a nitrogen atmosphere over a 3-hr period to a suspension of sodium hydride (100 g, 2.5 mol) in dry dimethylformamide (DMF) (1.2 l.) at 20°. After the addition was completed, the reaction mixture was stirred for 15 min at room temperature and then for 15 min at 50°. *n*-Pentyl bromide (300 g, 1.98 mol) was then added during 30 min. The reaction mixture was stirred overnight at room temperature, poured into water, and extracted thrice with ether. The organic layer was washed with a saturated solution of sodium chloride and dried over magnesium sulfate, and the solvents were removed *in vacuo*. Distillation through a small column afforded 2-pentyl-2-carbethoxycyclopentan-1-one: 284 g (64%); bp 100° (0.1 mm); ir